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Syringomyelia: with Autopsy Findings in Two Cases

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SYRINGOMYELIA: WITH AUTOPSY FINDINGS IN TWO CASES.

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The development of cavities in the spinal cord following apoplexy, traumatic hemorrhage, myelitis, embolic processes, or primary degenerations of the nervous tissues have not infrequently been described. In a number of instances in which a primary causative factor had been suggested for the condition the authors indicated that an inflammatory process and reactive gliosis had occurred secondary to the development to the cavity. The type of cavity developing in the cord is different in many cases, and this has led to a number of theories concerning the mode of origin. Moreover, the clinical history of the onset of these cases in adults is so divergent that it would appear that more than one factor was concerned in their development.

The majority of cases of syringomyelia have been described in association with gliosis, or as some prefer to call it, a diffuse glioma. Much attention has therefore been concentrated on this aberrant tissue of the cord. True gliomas of the cord without the presence of degeneration and cavity formation are known, while, on the other hand, there have been cases in which the development of a local or extensive cavity in the cord has been unassociated with primary changes in the glia.

The relation of syringomyelia to true tumors is particularly important in those cases where the gliomatous processes can be demonstrated to precede the cavity formation. In these conditions there is a definite mass of invading tissue which extends longitudinally in the cord and commonly involves the gray matter and the posterior columns. It would appear that the growth had its origin in the glia of the gray matter, but its subsequent extension not infrequently invades the white matter of the cord, where it displaces the various tracts.

The involvement is generally greatest in the posterior columns, but the tumor need not be confined to this region. Thus the entire cord may be infiltrated and destroyed in one segment, leaving little or no normal tissue, while in the segments both above and below this area the new-growth is confined to the tissues behind the commissure. At different periods of development the gliomatous mass may undergo softening, with partial absorption of the liquefied area. This softening is usually most extensive in the area of the greatest tumor involvement and in the areas of the cord occupied by the secondary growths. The absorption of the softened matter may lead to the complete disappearance of the cord in one or more segments. In other instances the main gliomatous mass continues to extend almost as rapidly as the central softening, with the result that the cord is occupied by a considerable tumor mass with an inner cavity. From the area of primary softening a similar process of degeneration follows the central portion of the infiltrating gliosis. Thus the column of new-growth occupying the posterior tracts comes to have a tubular cavity passing through it. Where the extension of the gliosis or tumor has followed several nerve tracts there may occur separate channels of softening. The process of softening is also accompanied by degenerative changes of the cells and tissue immediately surrounding the tumor tissue. Several investigators have indicated that the process of degeneration is associated with certain vascular changes as well as pathologic conditions in the enveloping membranes.

Under the general consideration of syringomyelia is included the discussion of cavity formation resulting from congenital anomaly. Such conditions are observed in cases where the spinal canal has been improperly closed, leading at times to the formation of a diverticulum which is still in communication with the spinal canal or where a channel near the posterior sulcus is independent of the central canal, and in no way communicates with it. Cavities of the former type are lined with a layer of columnar cells simulating the ependyma. It must, however, not be inferred that all cavities having such a lining membrane are of congenital origin. Some of the lesions of later life appear to acquire a similar lining.

The cases which are of the most interest are those which develop in adult life or at least in whom the symptoms first appear at this time. These cases have led to repeated controversies as to the primary factors in their origin.

Although, clinically, a group of symptoms indicative of syringomyelia has been described, not a few cases found at autopsy have presented symptoms of quite another character.

The following two cases of syringomyelia are of interest in indicating the mode of origin of their cavities, in the one case with and in the other without the presence of tumor.

Case I.—Mrs. R. M., aged thirty-eight years; housewife. The patient was admitted to the Pittsburgh Hospital September 19, 1910, under the service of Dr. J. D. Heard, to whom I am indebted for the clinical history.

On admission the patient complained of pain in the lower abdomen and along the spine, and inability to move the legs. The patient was the mother of nine children, and had been a healthy woman until last fall, when, after nursing her husband through a prolonged fatal illness she broke down. Moreover, at this time a number of subcutaneous abscesses developed in various parts of the body. Associated with this infection she had an acute attack of pain (acute pleurisy) in the left chest, which confined her to bed. She gradually improved, so that she was able to be up until the morning of her admission to the hospital. Suddenly upon that morning she found herself unable to move either leg. She was very definite in stating that this complete paraplegia took place within a period of two or three minutes. Since then the paraplegia has been complete. The patient was an emaciated female. There was a complete paraplegia, with loss of reflexes below the waist line. The bladder was distended to a point about an inch below the umbilicus, and contained 1000 c.c. of urine. Anesthesia was complete to all forms of sensation over the surfaces below a transverse line 3 cm. above the umbilicus. The left pleural cavity was the seat of effusion, which reached to a point opposite the seventh rib posteriorly. This effusion was rapidly absorbed, leaving behind an impaired percussion note.

Nervous System. Complete anesthesia over the area mentioned, which persisted until the end. There was no shifting or extension of the original area. The patient was never able to make the slightest voluntary movement of the legs, but during the last two weeks of her life, involuntary twitchings occurred in the anterior muscles of the thigh. There were marked trophic disturbances. Decubitus appeared over the sacrum about six days after admission. This spread rapidly, the tissue literally melting away. At the time of death ulceration had extended to the bone and measured 10 x 12 cm. There was also one over the inner side of the left foot and also an ulcer over the left hip. Control of the bladder or rectum was not regained. The urine toward the last became excessively fetid.

Laboratory Findings. The Wassermann test for lues was negative. Albumin was constantly present in the urine. From the first, granular casts, pus, epithelial cells, and occasional red blood cells were found. Leukocyte count varied from 12,000 to 21,400.

Clinical Diagnosis. The sudden appearance of the manifestations suggested the diagnosis of hemorrhage into the cord. Death was caused by pneumonia, sepsis, and exhaustion. An autopsy was performed one and a half hours after death.

Autopsy. The body was that of a middle-aged woman, 165 cm. tall. The skin surfaces were pale and the body was considerably emaciated. The pupils were narrow, the right being slightly larger than the left. Extensive and deep decubitus ulceration was seen over the sacrum, which extended to the bone, and measured 10 cm. x 12 cm. A round punched-out ulcer was seen over the left hip, exuding pus. A small fibroma was present in the skin of the right side of the neck. Some superficial ulcers were found over the heels and one over the inside of the foot. The genitals were negative. A small amount of blood exuded from the vaginal orifice. There was no postmortem rigidity of any of the muscles.

Thorax: No excess fluid was found in either pleural cavity. Some old adhesions were seen over the apex of the left lung and along the posterior border of the right lung. On bringing forward the left lung the lower lobe felt solid and was firmly adherent to the posterior thoracic wall. On removal the lung substance was torn by the adhesion. There was some purulent exudate enclosed by the adhesions behind the lung. This exudate was seen to burrow behind the parietal pleura and enter the intercostal space between the eighth and ninth ribs. An opening 1 cm. in diameter was seen in the pleura. Behind this opening was a larger cavity, from which pus could be expressed. This cavity was immediately over the angles of the ribs, and extended up and down, being 7 cm. in length. The ribs which formed the posterior boundary of this cavity were eroded on their inner surfaces. The pus cavity was 4 cm. in width and advanced to the bodies of the vertebræ. The right pleural cavity also showed some dense adhesions behind the posterior border of the lung, while in the retropleural tissues opposite the angles of the seventh, eighth, and ninth ribs was a shallow abscess cavity almost identical in size and appearance to that on the left side. These two abscess cavities had paths of communication across the vertebræ. The eighth and ninth ribs as well as the vertebræ opposite the abscess in the right side were denuded of their periosteum. There was a distinct lateral curvature to the left of the dorsal spine beginning at the seventh dorsal and ending at the first lumbar. The internal viscera showed nothing particularly of interest. A septic pneumonia was found in the upper lobe of the left lung. Extensive suppurative processes were present in the kidneys and urinary tracts.

Cord: On removing the cord some pus was noted about the vertebræ and on the outer surface of the dura in the region of the intervertebral foramina of the seventh, eighth, and ninth dorsal segments. The dura was decidedly thickened in this region. There was no evidence of inflammation nor of pus within the dura mater.

The pia was seen to be free from adhesions and exudate. Above the eighth dorsal vertebræ the cord was normal. Opposite the eighth and the upper part of the ninth dorsal vertebræ the cord did not present its normal contour, but instead of being firm and round it was soft and completely flattened. The flattening was due to the loss of the structure within the membranes. The pia mater over this area showed some injected vessels. The cord when cut through at the upper border of the ninth dorsal was disintegrated and structureless, and exuded a yellowish creamy material looking not unlike pus. Sections through the cord opposite the fifth, sixth, and seventh dorsal vertebræ showed the cord structure fairly intact, save for a small circular opening the size of the lead in a pencil, which on pressure exuded a pus-like material from it. There was no evidence of old or recent hemorrhage and no thrombosed vessels were observed. Examination of the pus-like material failed to reveal bacteria, and no cells could be found. The material consisted of a fine debris. Above the level of the fifth dorsal segment the cord was intact. Sections made through the tenth dorsal segment of the cord showed a number of necrotic-looking cavities in the posterior and lateral tracts, which contained a soft creamy debris. Sections through the eleventh segment showed a single cavity in the posterior tracts which only extended to about the middle of the segment. Below this level the cord showed no changes.

Microscopic Examination. Sections made from the eighth dorsal segment in the region of the greatest macroscopic change showed an almost complete necrosis of all structures within the cord. The area formerly occupied by the cord was replaced by a debris contained within the pia mater. Along a portion of the pia and apparently adherent to it was a thin layer of nervous tissue, showing much degeneration. This tissue could also be observed along the anterior sulcus where the pia with the bloodvessels was still intact. The central canal was to be seen and its lumen was patent. There was no evidence of a proliferation of the cells lining the central canal. The gray matter of the cord and particularly the anterior horns could be followed in outline, but showed extensive degenerative changes in its structure. A number of pyramidal cells showing chromatolysis were observed. On the other hand, the tissue of the posterior portion of the cord, including the white matter and the posterior horns, was disintegrated. Within these cord lesions there was no evidence of an inflammatory reaction. Leukocytes and lymphocytes were entirely wanting. Moreover, a careful study of the sections failed to reveal any evidence of thrombosed vessels within the cord. It was observed that in the small portions of the nervous tissue remaining opposite the severely damaged area the glia cells appeared more prominent than normal. These cells were to be observed as large spherical or at times irregularly shaped structures having very few processes. Some of the cells resembled endothelial cells, save that the nucleus was eccentric and occasional ones had short fibers. These cells were more prominent in the white matter than in the remains of the gray. Sections made through the fifth, sixth, and upper part of the seventh segments of the dorsal cord showed a fairly intact structure, save in the presence of a simple cavity lying immediately behind the commissure and slightly to the right side. This cavity occupied the white matter of the cord, and only bordered upon the gray. The tissue of the commissure was not involved, and although the central canal appeared to be narrowed the cells lining it did not enter into the formation of this cavity. The cavity was irregularly outlined and had no lining membrane. A necrotic wall without inflammation was its boundary. The tissue surrounding the cavity was loose and almost edematous. In places the large spherical glia cell was prominent, and although forming small aggregations, did not develop into masses. An irregular reaction in the glia cells of the white matter was to be observed in different portions of the cord. Immediately external to the posterior horns were seen occasional aggregations of large glia cells, which had developed immediately surrounding the bloodvessels. The diameter of the cavity passing upward toward the dorsal cord was not uniform but varied, at times occupying the entire width of the white matter lying between the posterior horns immediately behind the commissure. A similar but more irregular cavity formation was found in the segments below the level of the main lesions. In the tenth dorsal segment a number of irregular necrotic cavities were found in the white matter of the posterior columns, as well as in the lateral columns. The character of the cavities was similar, in that none of them had a lining membrane, but were bounded by a loose and partly necrotic tissue. In the eleventh dorsal segment a single cavity was present in the posterior columns.

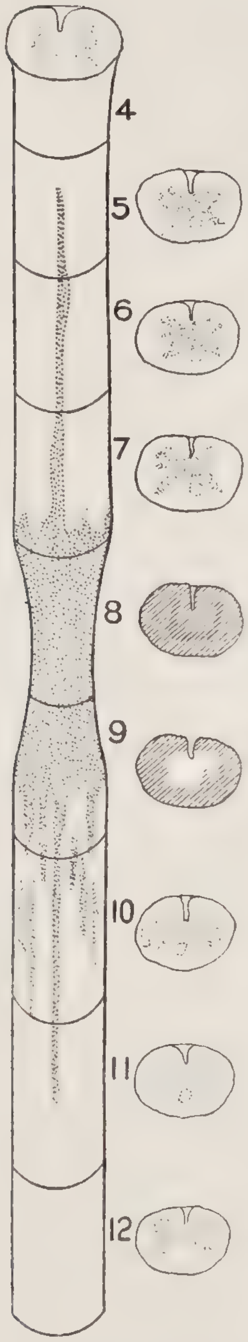

FIG. 1.—Cord of Case I, in which almost complete absorption of the eighth and ninth segment has taken place. A single cavity is seen passing upward, while multiple small cavities pass downward and enter the tenth and eleventh segments.

In no section was there any association of the cavity formation and the central canal to be observed. Sections of the dura mater showed a considerable thickening of the outer tissues and the presence of an infiltration by lymphocytes and plasma cells. The bloodvessels in the dura were the seat of an inflammatory reaction, but none of them showed a complete closure of their lumina. In only one vessel, a vein, was there found a recent adherent thrombus which was undergoing organization. The vessels lying immediately around the cord in the pia appeared normal.

Anatomic Diagnosis. Acute softening of the cord; syringomyelia; chronic pachymeningitis; chronic localized empyema of the thorax; interstitial abscess of the thoracic wall; unresolved pneumonia, with abscess of lung; old pleural adhesions; acute suppurative cystitis and pyelonephritis; trophic ulcers of skin.

The patient was suffering from a chronic pyemia and empyema in which the suppurative process of the thorax had extended into the spinal column and over the dura at the eighth dorsal segment. A decided inflammatory reaction was present on the outer surface of the dura, but it did not extend within this membrane. The sudden onset of the paraplegia, with complete loss of sensation, suggested hemorrhage or embolism of the vessels of this part of the cord. The microscopic examination showed no evidence of old or recent hemorrhage, and the lesion, which was the seat of extensive disturbance, consisted of an almost complete liquefaction and absorption of the cord structures at about the eighth dorsal segment. This cord destruction gave no indication of a true myelitis, nor was there evidence of new-growth. From this extensive and severe lesion there extended in both directions of the cord, cavities containing a necrotic material and outlined by irregular walls. One cavity extended upward into the fifth dorsal segment, while another passed downward as far as the eleventh dorsal segment. There was no evidence that the spinal canal was in any way involved or associated with the cavities, nor was there an ependyma lining them. In a number of sections a reaction was observed in the glia cells amounting to a proliferation of this tissue in the vicinity of the cavity formation. In other regions, however, changes in the glia were entirely wanting. The cavity formation involved mainly the white matter of the posterior columns.

Case II.—J. H., aged twenty-five years; laborer. The patient was admitted to the Mercy Hospital on January 16, 1912, under the service of Dr. G. O. Goulding. On admission the patient complained of the loss of the use of both lower extremities.

Previous History. About two weeks ago he did not feel well and noticed that his legs felt sore. He was able to walk on January 14 and 15, but on January 15, on attempting to get up in the morning, he found he was unable to walk or stand. He had no indication of the onset of this condition. Closer questioning of the patient revealed no detail of the present illness. He denied having had any accident or acute infection in recent years. At the time of admission there was a complete motor and sensory paralysis below the level of a line situated about midway between the nipple and umbilicus. The anesthesia was complete to all forms of sensation. There was no voluntary control of the sphincters or the bladder. As the patient had to be catherized, and although every care was taken to prevent infection, a cystitis developed about four weeks after admission. Further, large decubitus ulcers developed which were very deep and showed no attempt at repair. The patient gradually became septic, and died three and a half months after the onset of the paralysis.

Clinical Diagnosis. Acute transverse myelitis. Death resulted from sepsis.

Autopsy. An autopsy was performed sixteen hours after death. The body was 161 cm. in length and showed marked emaciation. Over the sacrum and both trochanters there were large ulcerating areas, which extended to the bones, and about 15 cm. of both femurs were exposed. The crest of the left ilium was exposed throughout its whole length. Over the chest and knees small round ulcers were seen.

Brain: The skullcap showed nothing abnormal. The dura was not thickened. The Pacchionian granulations were prominent. The hemispheres were of quite normal appearance on their surfaces. There was no evidence of exudate under the meninges. On opening the brain the ventricles were free from exudate. They were not dilated. The brain substance was a little pinkish, but showed nothing abnormal. The cerebellum was without change.

Cord: On opening the spinal canal no change could be observed about its bony structure or upon the outside of the dura. The dura was of usual thickness and its inner surface was smooth. There was no evidence of exudate upon the meninges. The vessels of the pia were injected along the posterior surface. The entire cord appeared swollen and larger than normal. The pia-arachnoid was tense and appeared to be stretched over the cord. In several places where the pia was slightly torn the cord substance bulged outwardly. The most marked change in the cord was between the seventh and eighth dorsal nerves, where there was an area of extensive softening which extended in both an upward and downward direction. Taking the middle point of the softening as existing between the seventh and eighth dorsal nerve roots, the softening of the cord, which involved the entire structure, extended 3.5 cm. in both directions, in which no structure could be made out. Smears from this softened material showed debris without the presence of any leukocytes. A greater or less change was to be noted in all portions of the remaining cord. Opposite the fifth dorsal vertebræ the cord structure was altered and showed the presence of a softer and whiter area occupying the posterior horns and all the tissues lying between them. What remained of the cord in this area was congested. At the level of the sixth dorsal a similar whiter and softer area was found, but here it was of greater extent. In this region the right anterior horn was also involved by the presence of new-growth. Similar areas of change were noted in the portion of cord below the softened tumor mass. At the upper extremity of the lumbar enlargement the cord was much congested and its markings indistinct. Here, again, however, the posterior portion of the cord was affected. In the pia, at about the tenth dorsal, was seen a small, flat, calcareous plaque.

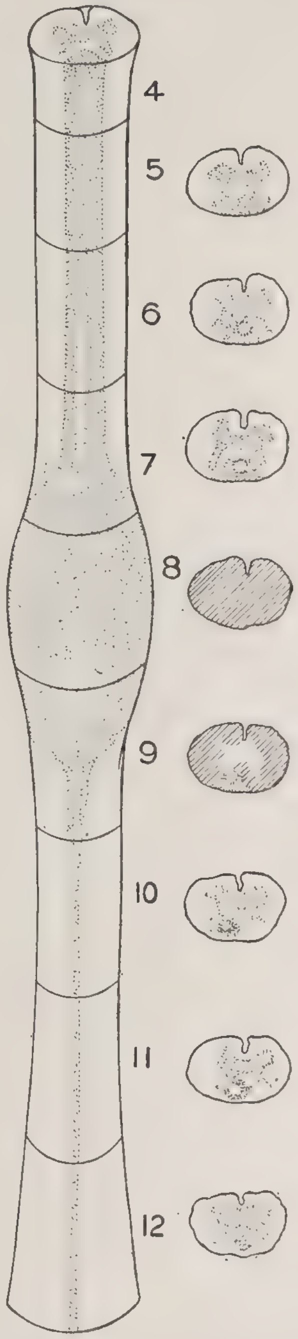

Fig. 2.—Cord of Case II, showing a gliomatous mass occupying the eighth and a part of the seventh and ninth dorsal segments. From this tumor a linear tumor mass passes upward and downward in the posterior columns. Within this extension of the tumor is found a process of cavitation.

Microscopic Examination of the Cord. Sections of the most involved portion of the cord showed a tissue in which normal cord structure could no longer be discerned. The tissue was composed of a fine reticulum and many irregularly distributed nuclei. In the reticulum there was a fine debris looking like degenerated reticular fibers. The nuclei were round and a little smaller than those of lymphocytes. Ganglion cells could not be found. In this tissue the reticulum appeared looser and almost vacuolated, as if a process of degeneration were present. There was, however, in this main tumor mass no evidence of cavity formation. This tissue occupied the entire cord at the level of the eighth segment. In the lower portion of the ninth segment a similar reticular tissue occupied the posterior columns and to a certain extent the lateral tracts. The gray matter was also encroached upon and its outline irregular. What remained of the white matter of the cord was much vacuolated and loose. The tissue occupying the area between the posterior horns showed evidence of degeneration and necrosis. Thus a mass of necrosis lay within the new-growth occupying the posterior columns. The new-growth could be followed through the succeeding segments of the cord down to its extremity, and within this area an irregular cavity of varying dimensions was present. In the lowermost segment of the cord the cavity was quite patent without the presence of the necrotic island observed elsewhere. The distribution of the tumor mass in the lower cord varied at different levels, but the main portion was found to occupy the posterior columns. The gray matter was variously involved. In the portion of the cord above the main tumor the invading glial tissue had followed the posterior columns. In places, however, other tracts were also invaded, but without any regularity. The invading tumor consisted of a loose reticular structure in which masses with more closely aggregated nuclei were observed. The tissue appeared quite vacuolated. This appearance was more apparent than real, in that many of the tumor cells were composed of large spherical cells with finely granular protoplasm. The reticulum consisted of fine threads associated with smaller cells with dark-staining nuclei. The tissue of the new-growth was quite vascular. The central canal showed a close aggregation of its nuclei and an apparent closure of its lumen. Opposite the eighth dorsal segment some tumor mass was also found in front of the right anterior horns. Extending through the tumor mass and always lying posterior to the commissure was a cavity which began in the seventh dorsal region and extended as high as the lower border of the fifth segment. This cavity had an irregular outline, with necrotic borders. Tumor tissue formed its outer boundary. There was no limiting membrane and tissue debris was found within. The bloodvessels in the vicinity of the tumor or of the cavity showed no evidence of thrombosis and no particular change was to be noted in the vessel walls. In some instances the coats of the small arteries appeared somewhat loose. New bloodvessels with thin walls were evident in the new-growth. In the sixth dorsal segment was found a small cavity isolated from the previously mentioned posterior channel, and apparently having no connection with other openings. This cavity formed an isolated area of degeneration in a small tumor mass, lying in the lateral tracts. The tumor which extended along the posterior columns was more extensive and far-reaching than the cavity formation.

Anatomic Diagnosis. Glioma of the cord with softening; syringomyelia; acute suppurative cystitis; pyelonephritis.

In the second case we are dealing with a man who previous to the onset of the present condition suffered no ill health or accident which might be associated with the lesion in the cord. Without any warning he suddenly found himself completely paralyzed from the waist down. The paralysis was permanent, and with it extensive trophic ulcers as well as sepsis, beginning in the urinary tract, led to his death some months later.

At autopsy a complete transverse destruction of the cord due to the invasion of a soft glioma was found. This new-growth not only occupied the original diameter of the cord, but even led to a tissue mass considerably greater than the diameter of the cord. This new-growth was situated at the eighth dorsal segment, and from this region the new-growth extended both upward and downward along the posterior tracts. It was in this new-growth that cavities developed by a process of degeneration.

In comparing our two cases it is evident that the cavity formation in the one is entirely different in origin from the other. In each instance, however, it is evident that the development of the cavity had been the result of a necrotic process and that the presence of the channels had in no way been related to the structures forming the central canal. In each instance the wall forming the cavity was ragged and formed by degenerated nervous tissue.

Moreover, no evidence could be found that hemorrhage played any part in the formation of these cavities. In fact, in neither case was there old or recent hemorrhage present.

The question which is of greatest interest concerns the way in which progressive cavity formation may take place in the cord. In considering the cases immediately under discussion we need hardly consider the question of syringomyelia occurring from anomalies of development. Such cases have been discussed by Virchow, and later enlarged upon by Seiden. It is of interest, however, that these authors believed that at times congenital cavities of the cord were followed by hemorrhage and softening as well as new development of glial tissue which would make them simulate the acquired types of the disease. It would, however, be preferable to retain the term hydromyelia for those cases in which the cavity had a development associated with the central canal.

Langhans offered an explanation for those cases in which the central canal alone was dilated. He believed that the process was the result of blood stasis in the posterior part of the skull which led to a venous hyperemia of the cord. The condition therefore simulated a transudate due to passive congestion. Under some conditions the process might later develop into a diverticulum.

The same view was held by Kronthal, who, however, indicated that the condition of passive hyperemia occurred in connection with processes within the spinal column as tumors, chronic meningitis, meningeal adhesions, or compression of the spinal cord. In general the theory of hyperemia found few supporters. Others have indicated that there was a relation between inflammatory thickening of the meninges and the development of cavities in the cord. Thus cases of acute cerebrospinal meningitis, with subsequent syringomyelia, are described (Saxer), while Phillips and Oberthur brought forward evidence showing the simultaneous development of thickening of the dura and cavitation of the cord.

In many of the reported cases of syringomyelia there was an associated spinal pachymeningitis, but its direct etiologic bearing on the cord condition is far from clear. In our first case a similar association was present, but here the pachymeningitis was clearly the result of an external inflammatory process, while the leptomeninges were not involved. The association of two conditions appears in this case coincident and not directly related. Moreover, autopsies not uncommonly reveal pachymeningitis, adhesions of the membranes, and various lesions of the cord without the process of spinal cavitation.

In those cases of hydromyelia in which the condition is one of dilatation of the central canal there is evidence of a secondary compression and atrophy of the surrounding nerve structures. In the majority of cases of syringomyelia symptoms of this character are entirely wanting.

According to Joffroy and Achard, syringomyelia bears no relation to hydromyelia nor to conditions arising from the central canal. They believe that it arises from chronic inflammatory processes in the gray matter of the cord, which later give rise to cavity formation. The destruction of tissue is particularly associated with circulatory disturbances, probably thrombosis.

The most widely accepted theory of the process is that of Simon and Schultze, which indicates a primary growth of the ependymal and peri-ependymal tissues of the character of gliosis. This development of new tissue progresses along the cord, while a necrosis with subsequent cavity formation develops in the inner and older portion of the growth until the true nature of the tissue can only be observed in the peripheral and distal portions. In some places the nature of the growth indicates a true glioma, and Weigert believes that a differentiation can be made between gliosis and glioma. Occasionally a communication may develop between the cavities of the new-growth and the central canal.

A number of cases of gliosis without the presence of tumor in the posterior columns of the cord have been described. Oppenheim discussed a case under the name of gliosis spinalis in which the symptoms had been those of tabes. The process extended from the cervical to the lumbar cord and occupied mainly the posterior portion of the gray matter. Here and there this tissue contained small lumina.

Against the contention that tumor development always precedes the formation of the new cavity in the spinal cord, Gerlach indicated that some cases showed no evidence of enlargement of the cord as we would expect from tumor, nor did the cord show the usual areas of softening as is seen about gliomas. The irregular position of the cavity as it occurs in different cases does not permit a common theory of origin.

However, it cannot be denied that in some instances the cavity formation was preceded by true tumor of the nature of glioma. This has been the condition in our second case. Thus we find the undoubted presence of a localized glioma which has increased the diameter of the cord and which in its oldest part has undergone softening. In the main tumor a cavity cannot be distinguished, and the whole mass is so soft that it cannot be handled without producing artefacts. In the further extension of the tumor, central liquefaction with partial absorption has given rise to cavity formation. Thus we have a well-marked glial tumor with secondary cavitation. But, on the other hand, there are cases in which the development of the cavity precedes a glial proliferation, while in a certain group of cases it is impossible to say from the nature of the tissue whether we are dealing with a glioma with extensive cavitation or with a primary syringomyelia having a considerable secondary gliosis.

Within the true tumors the thin-walled bloodvessels are prone to give rise to hemorrhage. At other times the vessels in and about the tumor undergo degeneration, with partial occlusion of their lumina. In these cases central necrosis of the tumor, with cavity formation, is not uncommon. It has been indicated by some that in the early stages of such tumor development, and before definite symptoms have arisen, there is a considerable chance of hemorrhage from trauma which otherwise would have been without harm.

Instances in which cavity formation had occurred subsequent to traumatic hemorrhage within a tumor have also been described.

On the other hand it is evident that cavity formation develops in the cord unassociated with tumor and apparently arising from varied processes. Thus it has been indicated that through primary hemorrhages, cystic cavities may develop, and that a not important cause for the long narrow channels is a progressive necrosis resulting from local vascular or circulatory disease (Westphal).

Thus we find that cavities may be present in the spinal cord under different conditions. These different forms are to be distinguished from each other as having a different mode of origin:

1. *Neuro-epithelioma Gliomatosis.* This is a true tumor having its origin in the cells lining the central canal. The tissue of the tumor is composed of glial cells with a fairly dense reticulum in which are distributed gland-like elements with lumina of different sizes (Rolly, Schultze, Kahler, Schlesinger, Ribbert, and Wright). Babes has indicated that the cells of the central canal sometimes show an inherent tendency to proliferate, giving rise to the ependymal adenomas. Hutchinson suggests that his second case, in which only a small cavity with an epithelial lining was found, had its origin in some misplaced ependymal cells which under certain vascular stimuli had developed into a cystic cavity.

2. *Diverticula of Central Canal.* A number of cases have been described in which an accessory canal communicating with the central canal of the cord has been found. These accessory channels are lined with the ependymal cells continuous with those in the central canal. The process is probably a congenital anomaly of defective closure (Jacoby and Kahler).

3. *Anomalies of Closure of the Posterior Sulcus.* At times a channel has been observed lying posterior to the commissure and having its walls composed of connective tissue. Some of these channels have been found to communicate with the surface, and it has been indicated that they result from an improper closure of the posterior sulcus in which some of the external membranes have been included (Jacoby, Gerlach). Thomas and Hauser's case probably belongs to this class.

4. *Degeneration of Gliomas.* The greatest number of cases of syringomyelia have probably been described under this class. It has usually been considered that the formation of a cavity within gliomatous tumors has been the result of necrosis from inadequate nutrition or of hemorrhage into the tumor, with subsequent absorption. Such cavities have a necrotic border of tumor tissue without a definite limiting membrane to the cyst. These tumors advance either along the gray matter or along the nerve tracts of the cord. This longitudinal growth may be rapid and the process of cavity formation within the tumor follow closely upon the development of the new-growth. Hyaline and other changes have been described in the walls of the bloodvessels of the tumor, and it has been assumed that these are predisposing factors for subsequent necrosis or hemorrhage.

5. *Primary Syringomyelia.* This class is a comparatively small one and includes those cases in which the cavity formation preceded a gliosis in the cord. In some instances the amount of change in the glial tissue was comparatively slight, while in others regenerative changes were extensive throughout the cord. The processes leading up to the formation of such cavities within the cord are various. Hemorrhage from trauma or spinal apoplexy (Kienboch, Brasch, Westphal, Spiller, and others), thrombosis or embolism of the spinal arteries (Chiari), venous and lymphatic stasis, acute toxic degenerations, changes in the spinal meninges (Japha, Oppenheim), leprosy (Dyer), an occulsion of the spinal canal have each been described as causative factors. As, however, the condition primarily bringing about the lesion in the cord does not lead to the death of the patient, the time that intervenes from the onset of the condition to the death of the patient permits of such further pathologic changes in the cord that a definite statement as to the initial cause of the lesion is often difficult to make. Thus, for instance, in our first case the clear-cut history would point to embolism or thrombosis of the vessels of the eighth dorsal seg-

ment (hemorrhage of the cord having been ruled out by the microscopic findings), and yet there is no positive microscopic evidence to establish the proof. The extensive softening occurring in the cord at the site of primary damage had also destroyed the contained vessels.

An examination of the tissues of this case also indicates that the cavity in the cord became progressively larger and that it continued to extend longitudinally. In other words the entire cavity did not develop at one and the same time. Why, by a process of necrosis and without the presence of an infiltrating tumor, such a cavity should continue to extend through the length of the cord has not been fully explained. It would appear that the process is intimately associated with the blood supply and the vascular anastomosis. In those cases where the spinal arteries have been occluded by embolism or thrombosis it is probable that thrombi continue to extend into the smaller branches and anastomoses of a particular region of the cord, and depending on the extent of the vessels involved, there develops a progressive necrosis with cavity formation.

The reaction occurring in the glial tissue in these cases of primary syringomyelia resembles an irritative hyperplasia. The irritant, probably the products of tissue degeneration, is too slight to lead to an inflammatory reaction, while, however, the cells of the immediate neighborhood respond in proliferation. Similar reactions in the glia are to be observed in the vicinity of cerebral hemorrhages.

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ARTERIAL LESIONS ASSOCIATED WITH RHEUMATIC FEVER.

By OSKAR KLOTZ.

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ARTERIAL LESIONS ASSOCIATED WITH RHEUMATIC FEVER.[1]

By Oskar Klotz.

From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.

(Plates XXIII.–XXIV.)

As our attention has been more and more centred upon the etiological factors associated with arterial diseases, we have had a better opportunity of studying each type in turn and of observing the various grades of intensity in which the particular process may occur. It is only by studying each process accurately that its importance in relation to the general subject of arterio-sclerosis can be determined. A number of such specific processes have received adequate attention, so that to-day we are familiar with at least the main points concerning them. Syphilis of the arteries has been well studied, and the effects of overstrain upon the arterial wall is well known in connection with particular systems. Moreover, we are familiar with the effect of occasional bacterial invasions upon the vessel wall, but the different results that may be induced by the same organism distributed in various parts of the body are not well determined.

Repeated suggestions of the harmful effect of certain bacteria upon the arterial wall have been made by clinicians, and these have, to a certain extent, been verified in animal experimentation.

The clinical evidence of arterial changes, though, in itself, indicative of pathological processes, gives no clue as to the actual lesion that has occurred in the artery. Furthermore, the mode of invasion, as well as the progress of the disease in the tissues of the artery, cannot be followed by the clinical evidence alone. On the other hand, it is difficult to correlate the pathological findings of arterial disease, with the actual factor causing it, if the pathological examination is not accompanied by a study of the disease in life, as well as a study of the agents which have been active in its production.

The association of rheumatism with diseases of the vascular system has been emphasised mainly by French authors. Rheumatic phlebitis, although rare, has been discussed in the works of Bouillaud (1840 [27]),

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Trousseau (1828 [28]), Legroux (1884 [29]), Lemaire (1864 [30]), Boinet (1899 [3]), Vaquez (1905 [26]), Achard (1900 [31]), and others, while inflammatory conditions of the arteries associated with rheumatism have been observed and reported upon by Leger (1877 [16]), Hanot (1896 [12]), Besson (1900 [2]), and others. Of these reports, however, only two (Leger and Hanot) have been amplified by autopsy.

Some have been insistent that a definite disease with clinical symptoms occurred in the aorta of patients suffering from acute rheumatism. Although they were agreed that the process was of an inflammatory nature, there was some discussion concerning the process by which the inflammation reached the vessel wall. Some claimed that the infection proceeded continuously from the affected aortic valves along the surface of the aorta. Others, however, indicated that such a process was not the common one, in that the abdominal aorta was not infrequently involved, and never showed a continuous intimal infection.

There has been considerable doubt as to the presence of inflammation of the peripheral arteries in which the *materies morbi* of rheumatism was the etiological factor. Some of this doubt has arisen because the majority of observations have been made clinically, and it has been contended that by this means alone it is impossible to differentiate the inflammatory condition from embolism and other processes. Quenille (1906 [32]) reports upon rheumatic arteritis, and indicates that others, Lemaire (1864 [18]), Fernet (1865 [7]), Lécorché (1869 [15]), and Lemoine (1869 [19]), have made similar observations. These reports, however, mainly clinical, deal with the acute stage of the process when the individual offers symptoms pointing to lesions of the arteries. On the other hand, Géneau de Mussy (1892 [11]) believes that many of the thickenings encountered in the arteries in later life are the result of rheumatic conditions following upon one or more acute attacks accompanied by fever. He reports the case of a young man, æt. 23, who for a month had articular rheumatism with endo- and pericarditis, and later developed thickening of the peripheral arteries.

Rheumatic arteritis appears in two clinical forms. On the one hand, it is a simple inflammation surrounding the artery and accompanied by localised pain and throbbing along its course. On the other hand, an inflammatory process begins from within, and an obliterating arteritis, which is also accompanied by localised pain, gives evidence of permanent obstruction of the vessel. These types differ, in that the former shows the inflammatory condition to be in the media and the outer coat, while the latter is a condition of primary endarteritis, associated with thrombosis or embolism.

Foajole (1866 [8]) reported this condition in a young girl, æt. 15, who in the course of acute articular rheumatism with endocarditis experienced a violent pain in the side of the neck. The author observed the increased volume of the right carotid as well as a gradual hardening of its walls. After a few days the pain disappeared, but returned after a fortnight. Besson reported the case of a man, æt. 23, who two years previously had an attack of acute articular rheumatism with heart disease. The patient indicated the region of the left subclavian where a definite throbbing, synchronous with the heart beat, could be observed. Later the condition resembled an aneurysm of the axillary artery.

Conti (1905 [5]) reported a similar case in a young man, æt. 17. He showed symptoms of thoracic and abdominal aortitis, as well as an arteritis of the left carotid. Barié ([2]) reported the case of a man, æt. 29, who during the course of a rather mild acute articular rheumatism developed a progressive pain in the right arm, which, at the same time, became swollen, heavy and throbbing. The vessel of the arm was thickened and on pressure caused pain. Gradually the right pulse became less, but under salicylates the condition improved.

In many instances it is difficult to rule out the diagnosis of embolism. Legroux (1884 [17]) reports the case of a girl, who at the age of 12 had her first attack of acute rheumatic fever. During convalescence she suddenly experienced a numbness in the left arm and forearm with a complete loss of function of this member. The pulse could not be felt. He concluded that an embolus had occluded the left brachial artery, which was very painful. In this case the acute rheumatic fever seems to have initiated the processes in the heart, which was followed by the occlusion of the left axillary artery by an infected embolus, giving rise to a localised arteritis and ending in aneurysm.

Roche and Burnand (1908 [24]) report the case of a man, æt. 30, who had long suffered from rheumatism. His first attack had occurred seventeen years previously, and since then he had suffered recurrent attacks, in each of which the heart was more or less involved. Recently, his heart failed to compensate for the severe lesions of the mitral and aortic valves. When seen by the authors, he was cyanosed and showed œdema of the lower extremities. He had continuous fever of moderate degree. After some weeks his temperature suddenly went up, and he complained of pain in the left arm, which continued to increase. In three days the radial pulse disappeared. Gradually a very small radial pulse was again obtained. After some weeks a mass appeared close to the upper humerus which was quite painful to the touch. Some time later the right arm became involved so that the radial pulse disappeared.

These authors believed that the clinical cases of rheumatic arteritis must be classified by analogy, comparing the clinical manifestations with the findings reported at autopsy. Leger and Hanot have described rheumatic aortitis, while Rabé ([23]) has studied rheumatic disease in the coronary artery. The latter described two principal lesions, one consisting of a proliferating endarteritis, the other of a diffuse mesarteritis. It is probable that the other peripheral arteries react in a manner similar to but milder than that in the coronary arteries.

The importance of the relation of such medial disease to aneurysm is also evident, and it must be recognised that the mesarteritis occurring in rheumatism may, at times, be so severe that various forms of ectases and sacculations may occur. In fact, in the reports of Feytaud (1906 [9]) we have evidence that an aneurysm developed in the aorta in consequence of a rheumatic infection. It would appear that aneurysms of the peripheral vessels are less frequent. Nevertheless, such have also been reported by Legroux (1884 [17]), Roger and Gouget (1907 [25]), as well as by Schmey (1905 [33]). Similarly Routier (1905 [34]) reported a case of acute aneurysm of the posterior tibial artery developing in the course of rheumatism.

The close relationship of peri-arteritis nodosa, with its aneurysms, and acute rheumatic fever, has also been suggested. It would appear that a fair number of these cases are associated with attacks of acute rheumatic fever. Thus, in general, one must consider acute rheumatic fever as a factor in the production of arterio-sclerosis, as well as of aneurysm.

In German and English literature less importance has been laid upon the association of acute rheumatic fever with arterial disease. Nevertheless, if we carefully study the reports of acute mycotic aneurysms such as have been described by Osler (1909 [22]), Eppinger (1887 [6]), McCrae (1905 [21]), and others, we find that not a few are the sequel of rheumatism, particularly where the disease had endocardial manifestations. The importance of acute vegetative valvular disease, affecting the mitral or the aortic cusps, in relation to an arterial involvement is particularly interesting.

Clinically this relation of rheumatism to heart lesions and the arteries has been studied by Feytaud (1906 [9]). He had the opportunity of studying five cases, but had no opportunity of making an autopsy on either of the two fatal cases. These cases described by Feytaud were clinically demonstrated to have developed aneurysms, and the very interesting feature concerning them is that the aneurysm in each case developed in the first part of the aorta. All of his cases occurred in children varying in age from 12 to 16 years. In one of them the aneurysm had ruptured.

There is, therefore, considerable evidence forthcoming indicating that acute rheumatic fever has a direct relation to arterial diseases.

On a previous occasion (1912 [13]) we have pointed out how commonly the effect of acute rheumatism is to be observed in the arterial tree. In this communication it was shown that the results of acute rheumatic fever may be distinguished in the arterial wall during the primary acute attack, the recurrent acute attack, as well as in the chronic stage of the disease. It was also indicated that each of these stages could be recognised with fair accuracy by the character of the inflammatory reaction present in the arterial wall. Thus we might say that the arterial lesion simulates in many respects the inflammatory manifestations present in the myocardium. We were impressed with the fact that certain portions of the arterial system are as frequently attacked in rheumatism as in the musculature of the heart.

In our first report we presented the results of three cases of acute rheumatic fever (first attack), four cases of recurrent rheumatic fever, and eight cases of chronic rheumatism. Since this report, we have further followed the pathological lesions occurring in new cases of rheumatic fever, particularly observing the character of the lesions in those dying during the first attack of this disease. Our findings in these latter cases is similar to that previously reported. We have found, however, that the type of inflammatory exudate is not as constant in character as was originally observed.

The lesion is essentially an inflammatory one which is present in the adventitia and media of the arteries. The intima is not disturbed, save as a late secondary reaction over the inflamed media. The inflammatory exudate is mainly distributed about the vasa vasorum of the adventitia and follows the fine nutrient vessels lying in the outer portion of the media. This reaction is accompanied by a destruction of the neighbouring muscle cells and elastic fibres. The extent of this destruction is dependent upon the intensity of the reaction (Plate XXIV. Figs. 3 and 4).

This very feature, the intensity of the reaction, we have found to vary quite widely, and thus too, as we have indicated above, does the character of the inflammatory exudate differ. In our early cases where the reaction was moderate the exudate consisted mainly of lymphocytes and plasma cells. Latterly, we have found, and particularly in association with a case presenting an aneurysm, that polymorpho-nuclear leucocytes may also be present in large numbers in reaction. The presence of fibrin in the uncomplicated lesions we have not observed.

Another point upon which we must lay some stress has repeatedly presented itself in our studies. This is, that the point of predilection in acute arteritis, associated with acute rheumatic fever, is the ascending limb of the aorta. Though we have observed inflammatory reactions in other portions of the aorta and a few instances about some of its branches, these results were inconstant.

We have previously suggested the similarity of these lesions to those found in the early stages of syphilitic aortitis, and the obvious suggestion that these diseases might run a fairly similar course presented itself. One very decided difference, however, must be recognised between the syphilitic disease of the aorta and that of rheumatic origin. In the former, the process about the vasa vasorum when once begun is progressive, so that the media becomes more and more involved in its neighbouring parts. It would appear that in syphilis the disease rarely comes to a standstill, at least in as far as the recognised and studied cases indicate. It may be that with the newer treatments this view must be modified. In rheumatic disease of the aorta the process usually comes to an end spontaneously, but always predisposes the involved areas to recurrent attacks.

Recently Fukushi (1913 [10]) has described what he believes to be a characteristic lesion for syphilis in the aorta. Not only does the inflammatory reaction occur mainly in the adventitia and the media, but the cells of the exudate consist mainly of plasma cells and lymphocytes. This author has been so impressed by the abundance of plasma cells in the syphilitic lesions of the aorta that he believes their presence is indicative of the specific nature of the infection. Although the actual number of plasma cells has not drawn our particular attention, we have always observed their presence in the arterial lesions associated with acute rheumatism, and we are not inclined to believe that these cells serve the diagnostic purposes suggested by Fukushi.

The fibroses which are present in the adventitia as well as the media of the aorta in elderly individuals are not uncommonly the late effects of acute rheumatic fever, and if we compare the findings of Koester (1875[14]) and his pupils in arteriosclerosis with these observations, one is struck with the similarity of the processes described. Koester paid little attention to the etiological factor which induced the inflammatory reaction of the media which he viewed as being so important in subsequently leading to intimal thickening. We believe with Koester that, in as far as the inflammatory processes of the media associated with rheumatism are concerned, the intimal thickening is secondary.

Although it is the tendency for the inflammatory lesions of acute rheumatic fever to heal in a process of fibrosis, yet in a number of cases the arterial lesion is distinctly progressive, the destructive changes being so rapid that repair is impossible. In these instances the process developing in the outer portion of the artery continues to bring about destruction of the fixed local tissues until the strength of the vessel wall is greatly impaired. In these instances the inflammatory reaction spreads from its primary location about the vasa vasorum until several of the involved areas coalesce. The degree of inflammation being more acute, causes a more rapid melting down of the tissues. Aneurysm with or without rupture is the end result.

Such a case beginning in acute rheumatic fever with cardiac involvement and ending in a saccular aneurysm of the ascending aorta has come to our notice. We have given rather extended notes upon this case in order that we may offer convincing proof of the intimate relation of acute rheumatic fever to severe arterial disease.

We are much indebted to Dr. O. M. Edwards for the clinical history of this case.

Clinical History:—The patient was a boy, æt. 6 years, who had been quite robust, although he had had measles, chicken-pox, and whooping-cough. Six and a half months ago (September 1911) he became ill with symptoms simulating typhoid. His temperature, varying from normal to 104° F., continued, along with some indefinite muscular pains, and pains in the joints. Early in December he had some severe pains in the region of the heart and his joints, the elbows being particularly painful.

When admitted to the hospital on 1st March 1912, the child was suffering from severe precordial distress, pains in the joints, and choreiform attacks. The child was so restless that to examine him was very difficult. The heart was enlarged, the right border extending 1½ inches to the right of the sternum. At the apex both heart sounds were distinct, but over the pulmonary area a systolic murmur obscured both sounds. Over the aortic cartilage a loud systolic murmur was heard, but the second sound was not distinguished. Pulse, 140; hæmoglobin, 45 per cent.; leucocytes, 18,000. The urine contained albumin and granular casts.

For the next few days the child was very fretful and complained of severe pains in the joints and about the heart. The systolic murmur of the heart could be followed from the aortic cartilage along the great vessels of the neck. A blood culture showed a pure growth of a streptococcus growing in short chains. This organism was not studied on differential media.

Four days after admission the child died.

Autopsy.—At autopsy the chief findings were associated with the circulatory system. No important changes were found in the other organs, save the presence of infarcts in the spleen, and both kidneys. These infarcts were recent as well as old, in the latter some fibrosis was evident.

The heart was relatively large. The muscular walls were fairly firm. The left heart occupied much the greater part of the whole organ, and the apex consisted of the tip of the left ventricle. The apex was somewhat rounded; in fact, the whole was globular. The pericardial surface was for the most part quite smooth, but at the base, and particularly over the auricles and around the great vessels, there was a fine granular exudate of fairly recent lymph. At the base of the organ a portion of the pericardial sac was found adherent to the first part of the aorta. On the external surface the vessels of the heart appeared normal.

The right heart appeared quite healthy. There was but little blood within its chambers, and the tricuspid and pulmonary valves were without change. The musculature of the right auricle was rather pale but not thickened.

The left heart appeared out of proportion in size with the right side. The auricle was not enlarged, although the endocardial lining of its cavity appeared white and thickened. The left ventricle was large. The musculature was thick, and measured from 1 to 1·75 cm. The cavity itself was also large. The musculature of the left ventricle was pale and rather streaked. Some of these streaks showed fine lines of congestion or hæmorrhage. The mitral valve was of usual size. The cusps were a little œdematous along the free edge and both showed some granular vegetations. The mural cusp showed evidence of previous inflammatory processes in the presence of some erosion and fibrous thickening. The recent vegetations consisted of granular fibrinous deposit which could easily be removed.

The aortic ring showed extensive change. The normal architecture of the valve was entirely lost. Of the valve leaflets, only one could be distinguished. The area previously occupied by the other two cusps was filled in by massive fibrinous deposit, which distorted the aortic opening and almost occluded it. The deposit of this inflammatory exudate was accompanied by erosion of the surrounding tissue, including some of the mural endocardium just below the aortic ring at the base of the mitral valve. The exudate was confined to a strip of tissue about half a centimetre in width directly over the aortic valves. The openings of the coronary arteries were to a certain extent encroached upon by the vegetations on the valves. Immediately above the sinuses of Valsalva there was a portion of the base of the aorta which was quite free from acute disease.

The aorta presented a most remarkable condition. In the ascending limb, and situated upon the posterior surface but projecting slightly to the right, was a bulging mass the size of a pigeon's egg, measuring 2·5 × 2 × 1·5 cm. (Plate XXIII. Fig. 1). When viewed from without, this mass was found to lie within the pericardium, but to it the parietal pericardium was found to be adherent. The mass projected as a mushroom-shaped tumour, and was quite injected on its outer surface, so that its boundaries were easily distinguished. Immediately beyond the point of attachment of this mass to the aorta the tissues were quite pale. When viewed from within, it was seen that the projecting mass was due to a circumscribed bulging outwards of the aortic wall. The aorta was involved in this dilatation by about two-thirds of its circumference. The transverse portion of the arch of the aorta was not involved. The saccular dilation began suddenly on all sides, and its cavity contained a considerable amount of fibrin deposit, which had a rough and nodular appearance. At the lower margin of the saccular dilatation the intima of the vessel showed some pearly thickening. The remaining part of the aorta and the large systematic vessels appeared to be quite free from macroscopic change.

Bacteriology.—At the autopsy a culture was taken from the blood and the spleen, and in each instance a streptococcus growing in short chains was isolated. The individual organisms commonly arranged themselves in pairs.

Heart.—Sections were made from the various parts of the heart muscle. It was found that irregularly distributed through the musculature and more particularly through the walls of the left ventricle there were aggregations of inflammatory exudate consisting of polynuclear leucocytes, lymphocytes, and plasma cells. These inflammatory infiltrations were most evident in the regions of the small nutrient vessels of the heart muscle. In the vicinity of these reactions the heart muscle showed evidence of degeneration, and at times considerable areas of heart muscle consisted of indefinite wavy fibrils which had lost their staining qualities. In places these areas of degeneration showed some replacement by connective tissues. Fragmentation of the nuclei of the muscle cells was commonly observed in the areas where degeneration was progressing. In the vicinity of the areas of degeneration the muscle nuclei yet remaining appeared much larger than elsewhere.

Aorta.—Sections of the ascending branch of the aorta taken a short distance from the aneurysm showed a healthy character to the intima as well as in the media (Plate XXIV. Fig. 2). There was, however, observed in the tissues of the media an occasional inflammatory infiltration around the vasa vasorum of the outer third of the vessel. This exudate consisted mainly of lymphocytes. In the vicinity of this infiltration some disturbance of the muscular and elastic tissue elements of the media was observed. The adventitia of the ascending limb of the aorta showed quite an extensive inflammatory infiltration around the vasa vasorum of all sizes. In some places this infiltration was composed for the most part of leucocytes, in other places lymphocytes and plasma cells were predominant. Although the infiltrations were quite extensive, no destruction of tissue was observed in the adventitia. There was no evidence of anything simulating abscess formation. In some of the small vessels of the adventitia proliferative changes could be seen in the intima. Occasionally a few fibrin threads were present in the vicinity of the inflammatory reactions.

Sections obtained in closer proximity to the aneurysm of the aorta showed characters similar to the above, but of greater intensity. The infiltration about the vasa vasorum in the adventitia was more marked, and the inflammatory reaction extended more deeply into the aortic wall along the paths of the nutrient vessels. A greater number of leucocytes were present in the exudate in the media, and about these reactions the vessel suffered severely. The muscular elements were destroyed and their place was taken by a granular débris. The elastic tissue elements were swollen and distorted, so that they no longer retained their parallel arrangement. The inflammatory exudate led to the production of wide spaces between the altered elastic fibres. The greater amount of change was in the outer third of the aorta, but inflammatory products were also present in the inner part of the walls. Close to the aneurysm the entire wall of the aorta was seen to be infiltrated with polynuclear leucocytes. The leucocytes followed the spaces between the elastic laminæ and gradually displaced the muscle elements. In places the elastic fibres were also destroyed so that only fragments of them remained. At the mouth of the aneurysm it was seen that the intima and the greater part of the media had been destroyed and these coats came to a sudden end. The outer portion of the media was everted and dragged along with the adventitia, which formed the saccular pocket of the aneurysm. The wall of the aneurysm was formed by the adventitia with a narrow margin of the media, and was reinforced on the outside by the adherent portion of the pericardium. The sac of the aneurysm contained an adherent fibrinous clot in which numerous leucocytes were found. The greater number of leucocytes were found upon the surface of the adherent blood masses within the aneurysm.

Here and there along the wall there was some attempt at organisation of the inflammatory exudate. There was no evidence of abscess formation in any part of the tissue. On the surface of the intima, close to the aneurysm, there was some adherent blood-clot. The intima appeared slightly œdematous and thickened beneath this attached clot.

Bacteria were demonstrated in the tissues showing the acute inflammatory reaction. These were of the nature of Gram-positive cocci, appearing singly, sometimes in pairs, and rarely in short chains.

The above case is clearly one of an acute saccular aneurysm, occurring at an unusually early age (6 years). The clinical course of this disease was that of acute rheumatism in which the heart had suffered severe valvular disease. The inflammatory process in the aorta simulated in every respect the lesions as we had described them for acute rheumatic fever in a previous article. In this case, however, the destructive feature and the acuteness of the process in the arterial wall was much greater than any we had previously observed.

The development of aneurysm in acute rheumatic fever simulates the process in syphilis in as far as the inflammatory invasion begins in the adventitia and the vasa vasorum of the media. Syphilis was not to be thought of in this case, in that the arterial process was too rapid in its development. The inflammatory exudate was, in part, of a polymorpho-nuclear character, and there was no evidence of fibrosis in the vicinity of the damaged areas in the artery. Moreover, the secondary intimal reaction with its nodular thickenings as it occurs in syphilis was not present, and a type of streptococcus was demonstrated in the affected tissues.

When it is appreciated that acute rheumatic fever attacks the arterial system as an inflammatory process of varying degree, one may readily understand the finding of arterial damage of all grades of intensity. It is probably more common to meet with the more simple inflammatory processes than the more intense ones, which act so severely upon the artery as actually to weaken its walls. Nevertheless, it is more than probable that the subsequent fibrosis plays some part in bringing about the progressive changes in later life.

The repeated observation that systematic bacterial invasion is prone to attack the ascending limb of the aorta still remains without adequate explanation. It has repeatedly been impressed upon us that when the bacteria themselves are making inroads on the vascular tissues, they do this by attacking them by the way of the vasa vasorum. It is only when bacteria are carried in larger emboli or are caught in thrombotic masses that they attack an artery from the surface of its lumen. Moreover, it is much more common to observe this bacterial invasion in the ascending aorta, than it is in any other portion of the arterial system. In confirmation of this we need only refer to the processes induced by syphilis (Heller, 1903 [35]) (Chiari, 1903 [4]), influenza (Marmorstein, 1908 [20]), rheumatism (Feytaud, 1906 [9]), typhoid and streptococcal septicæmia.

It is possible that in a number of cases the ascending aorta may become involved in an inflammatory process by the direct extension of the disease from the aortic valves upon the surface of the aorta. This mode has been suggested for a number of cases of acute mycotic aneurysm, in which acute valvular disease was present in the heart. This primary invasion of the lining membrane of the aorta was suggested by the continuous layer of exudate from the involved aortic valve to the aneurysm. In not a few cases, however, as well as our own, there was a strip of healthy aorta lying between the valvular disease and the aortic aneurysm. From the presence of the great damage in the external zone of the aorta, as well as the constant finding of inflammatory foci of lesser degree in the outer part of this vessel, we feel convinced that these aneurysms have their beginning in the progressive destruction in the outer portion of the arterial wall.

In conclusion, it is important that greater attention be given to the various types of acute aneurysms and their relations to acute rheumatic fever; and, further, that the almost constant presence of some inflammatory reaction in the ascending limb of the aorta be recognised as an associated condition in this disease.

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DESCRIPTION OF PLATES XXIII.-XXIV.

Plate XXIII.

Fig. 1.—Acute mycotic aneurysm of ascending aorta in a boy of six years, suffering from acute rheumatic fever.

Plate XXIV.

Fig. 2.—Section of the aorta at the border of the aneurysm (Fig. 1), showing the acute mesaortitis and periarteritis with rupture of the inner arterial walls.

Fig. 3.—Acute rheumatic mesaortitis and periarteritis. (Boy æt. 14 with acute rheumatic fever.)

Fig. 4.—Acute rheumatic mesaortitis and periarteritis. (Boy æt. 17 with recurrent rheumatic fever.)

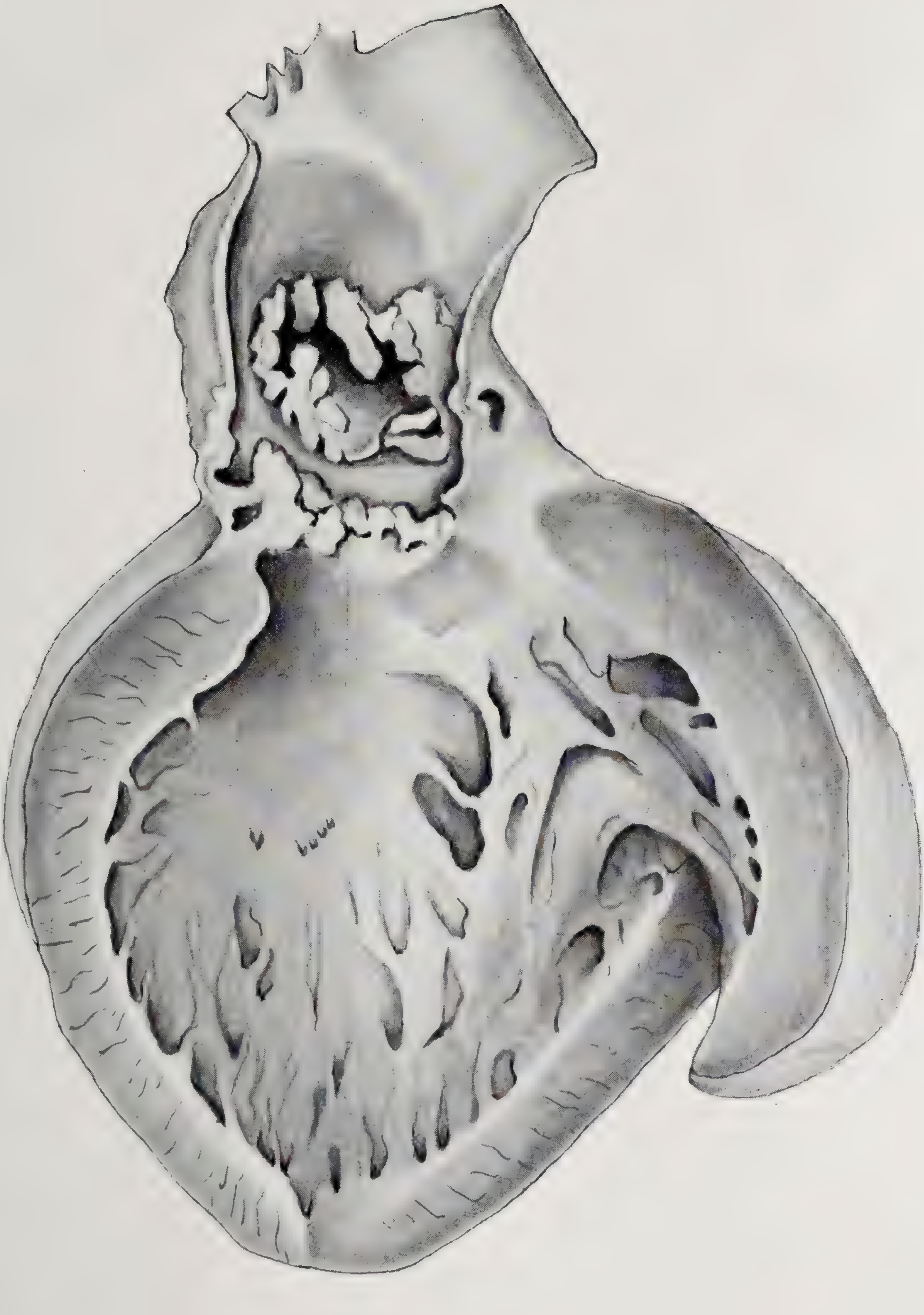

FIG. 1.

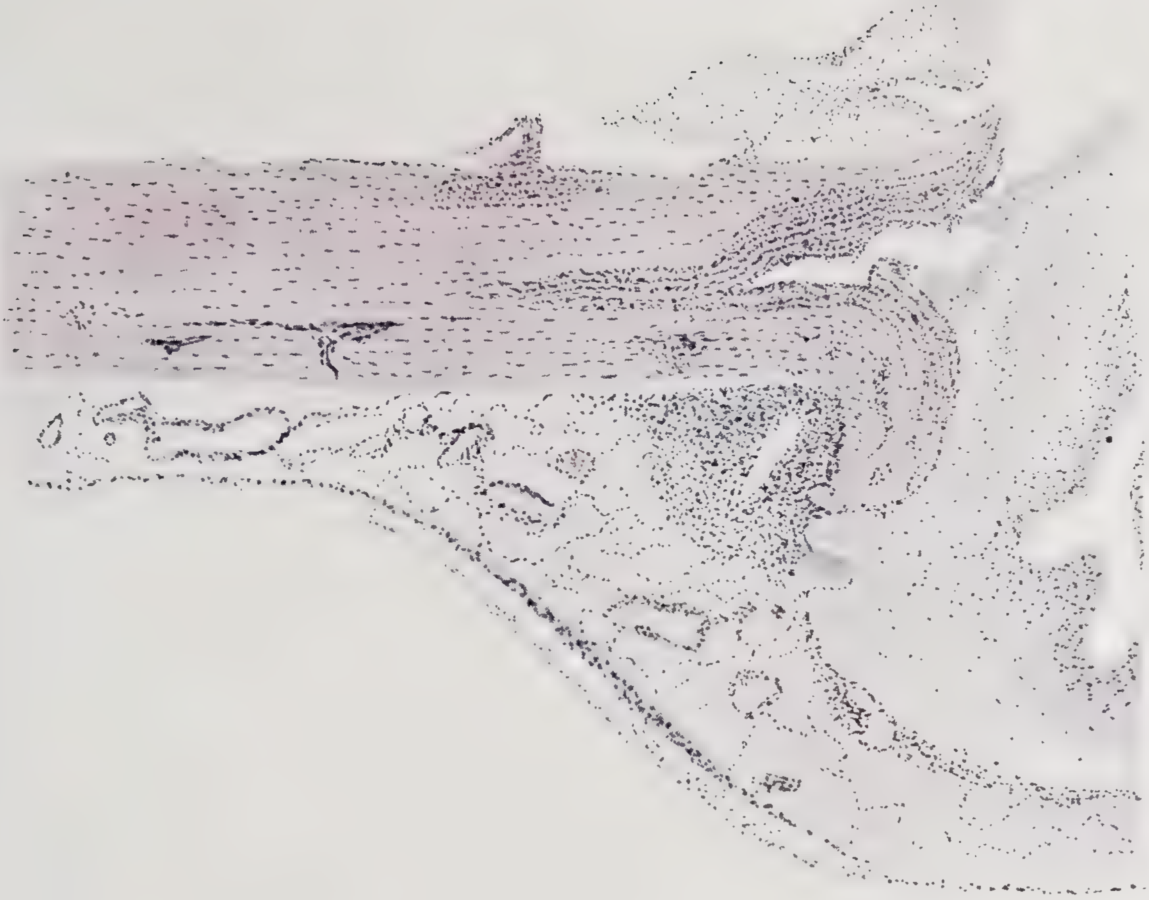

FIG. 2.

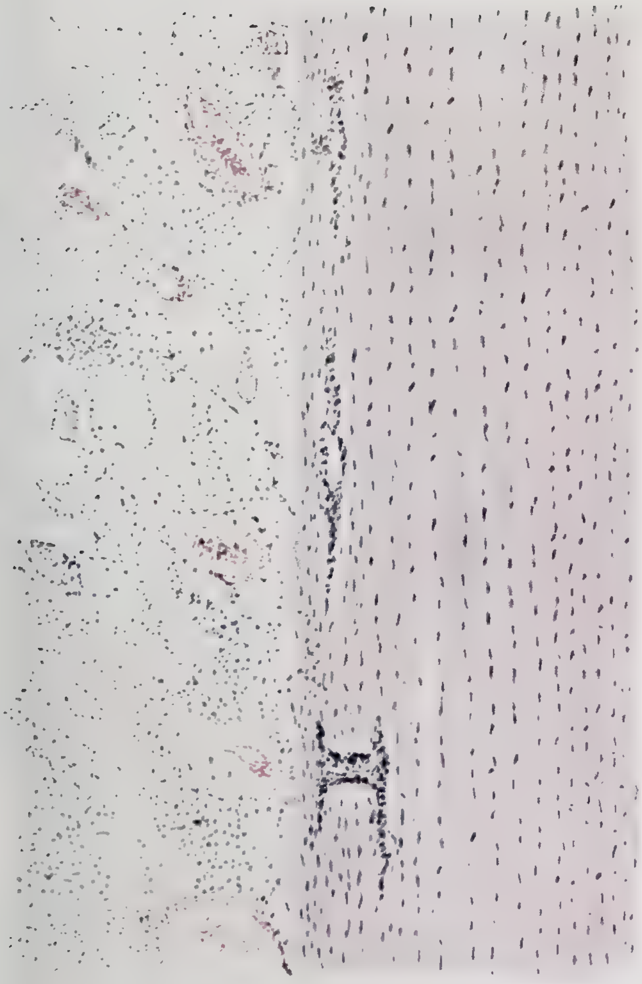

FIG. 3.

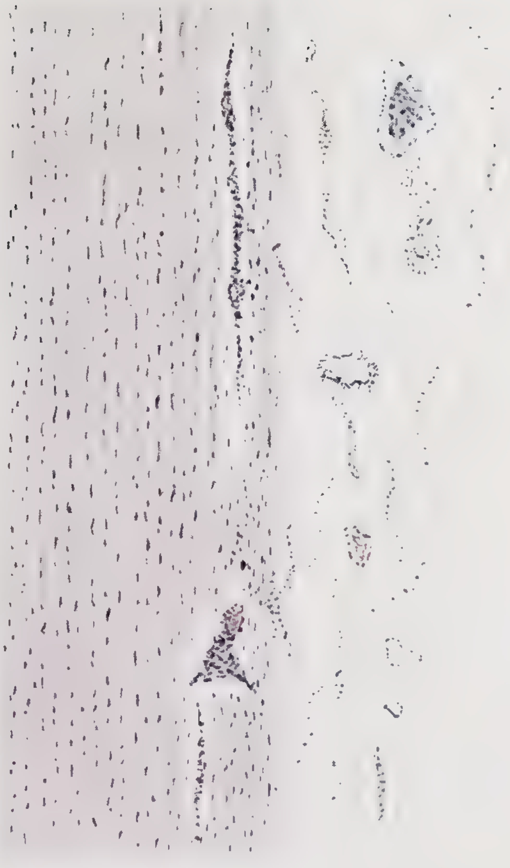

FIG. 4.

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RHEUMATIC FEVER AND THE ARTERIES

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Cardiac lesions are no longer considered as complications of acute rheumatic fever, but are just as much a part of the disease as the affection of the joints. The frequency of the association of pericarditis, endocarditis, and myocarditis or any one of them with other lesions making up the picture of acute rheumatism is very great, and I think many will agree with Aschoff that every attack of rheumatic fever leaves its mark on the heart. It has been particularly emphasized that the myocardium is most often affected, and this for the reason, as we shall subsequently indicate, that the reactions to rheumatism occur in the neighborhood of the fine nutrient vessels of the myocardium. Inflammatory exudates occur about these fine arteries, and are replaced in the chronic stages of the disease, by fibrosis.

In general our conception of acute rheumatic fever is being modified with the progress of the pathological studies made upon it. That it belongs to the acute infections no one will deny, and many are willing to place a considerable stress upon the organism of Poynton and Paine as the causative agent. Whether it is the initial factor, or whether some other condition predisposes to the invasion of the diplococcus rheumaticus, we cannot here argue; but it is more than probable that the lesions as we find them in diverse parts of the body are the result of the action of these diplococci.

In the late stages of the disease process we not infrequently observe the association of heart, kidney, and arterial lesions making up a picture very different from that of acute rheumatic fever.

Nevertheless we are compelled to admit that all of them are either the result of the primary acute process or else that in the process of a vicious circle one lesion has followed the other. A close study of the various organs can alone determine the direct effect of this systemic disease upon each, and with this in view I have followed, in a few cases, the lesions to be observed in the arteries and more particularly the aorta during the course and different stages of rheumatism. This study presents purely the pathological side of the question. The cases studied were selected from a series of autopsies, only those being taken in which one or more previous attacks of acute rheumatic fever were established in the clinical history and in the presence of interstitial myocarditis.

In classifying the cases here examined I have divided them into three groups: (1) Acute rheumatic fever, first attack; (2) recurrent rheumatic fever, and (3) chronic rheumatism. It was interesting to find that the changes in certain arteries were analogous to the lesions found in the heart in the different stages of the disease; in fact, the resemblance of the inflammatory reaction in the aorta to that of the myocardium was very great. It may, however, at the very beginning, be pointed out that the causative agent of acute rheumatic fever has a predilection for the perivascular tissues of the smaller vessels, the arterioles, and does not appear to disturb the larger arteries directly, save by damage in the vicinity of the vasa vasorum. Up to the present I have not made a systematic study of the arterioles of all the viscera of the body. My observations have, however, indicated that the arterioles of the internal organs, except the circulatory system, are not attacked with any constancy.

The aorta shows a fairly typical lesion. This lesion is particularly to be observed in the ascending limb and in the arch, less frequently in the descending thoracic and seldom in the abdominal aorta. The distribution of the process in the aorta is similar to that of syphilis, and, as a matter of fact, to that of many bacterial infections. The main coronary arteries of the heart are inconstantly involved, while, on the other hand, the finer ramifications of this vessel are invariably affected, being a part of the myocardial disease which forms an important factor in the pathological picture of rheumatic fever. Moreover, the arterioles passing to the serous cavities, particularly the pericardium and the joints, partake of a reaction similar to that of the nutrient arteries of the aorta and heart. In how far the vessels of the meninges and the abdominal viscera respond to the irritant present in rheumatism I am not prepared to say.

Acute Rheumatic Fever (First Attack). Of such cases I have had only three to autopsy, aged nine, sixteen, and nineteen years respectively. All of them had associated cardiac disease, two with pericarditis, all with acute interstitial myocarditis, two with fresh mitral deposits, and one with recent mitral and aortic vegetations. The youngest case had suffered choreiform attacks during his illness.

The arterial findings being similar in these cases a single description will suffice. Macroscopically the arteries were but little changed, the oldest individual alone showing superficial fatty streaks in the intima. The elasticity of the aorta was not altered and none showed the inflammatory foci to the naked eye. Microscopically, however, there was a very striking picture present in each case. Sections of the ascending and transverse portions of the aorta showed that the intima was not thickened and the lamellæ of the media appeared regularly disposed. In the media, however, the arterioles appeared more prominent than usual, and these nutrient vessels encroached beyond the outer third into the muscularis. These arterioles had an edematous perivascular infiltration in which aggregations of lymphocytes and plasma cells were constantly found. Moreover, the elastic fibers of the media in this vicinity were interrupted, often appearing as if mechanically broken. Muscle elements of the media in the neighborhood of the vasa vasorum had also, in part, disappeared, an indication of some local toxic agent surrounding the nutrient vessels.

In the adventitia the infiltration by inflammatory cells was very extensive. Lymphocytes and plasma cells were diffusely scattered through the tissue, while more densely aggregated cells were seen about some of the vessels. Polymorphonuclear leukocytes were also seen, but in relatively small numbers. Occasionally areas indicating endothelial proliferation were observed in the vicinity of the capillaries. The connective tissue was loose and rather edematous, while the capillaries were much congested. In some of the reactions fibroblasts were apparent, but no new connective-tissue fibers were observed.

The main coronary arteries of the heart were but little affected, save at the periphery of the adventitia. The smaller arterioles, however, showed a dense infiltration about them, with a considerable change in the appearance of the heart tissue in the immediate vicinity. In places the infiltrating cells were mainly lymphocytes, while in others again leukocytes and endothelial cells appeared to make up the main type of invading cell. The heart muscle adjoining these involved vessels showed evidence of degeneration and not infrequently complete death. In the place of these heart muscle cells there remained a homogeneous and almost structureless material with occasional evidence of replacement by fibroblasts. The perivascular infiltration was very widespread and quite uniform throughout the heart muscle.

It is indicated in the above that the main reaction occurring about the arteries during the acute stage of rheumatic fever is in the outer coats. The adventitia and the media are probably simultaneously involved, at times by way of the nutrient vasa vasorum, or in the case of the smaller vessels, the arterioles, directly from the perivascular lymph stream. The reaction is of the acute non-suppurative variety, in which the lymphoid type of cell and the endothelial cells play the important part. Similar to the reaction in the heart, the tissues of the arteries suffer directly from the harmful agent of acute rheumatism, in which both muscle cells and elastic fibers in the immediate neighborhood are destroyed.

Recurrent Rheumatic Fever. Four cases of recurrent rheumatic fever were studied. Their ages were twenty-eight, thirty, thirty-six, and forty-four years respectively. In each case there was a history of one or more previous attacks, and the heart showed the presence of subacute and chronic interstitial myocarditis to a varying degree. Moreover, some form of recurrent endocarditis was present in each heart.

Sections of the aorta showed the intima to be fairly intact and with no definite areas of thickening. The arrangement of the media appeared quite normal and regular in its inner half. However, it was observed that the vasa vasorum were quite frequent in the middle third of the media, and that these small bloodvessels were surrounded by an excessive amount of fibrous tissue, along with a cellular infiltration consisting of lymphocytes, plasma cells, and a few endothelial cells. This perivascular infiltration was quite constant, and at times the aggregation of wandering cells was quite marked. In some areas it was definitely indicated that some of the muscle cells and elastic fibers had been destroyed and their place taken by a meshwork of new connective tissue. Polymorphonuclear leukocytes were for the most part wanting.

The adventitia also showed a lymphocytic infiltration around the vasa, as well as an increase in the connective tissue close to the media. Some of the nutrient vessels showed a thickening of their walls with a narrowing of their lumina.

It is evident that in these cases of recurrent rheumatic fever certain changes have been produced about the aorta, which subsequently lead to an increase of fibrous tissue in the outer portion of the media and in the adventitia. Moreover, it would appear that with each recurrent attack of the disease a new non-suppurative inflammatory reaction occurs in the sites of the former lesion. Therefore in the recurrent types of the disease various stages of the inflammatory process may be observed in the same specimen. The former attacks are indicated in the presence of adult connective tissue, while the recent progressive condition is seen in the non-suppurative inflammatory infiltration.

Chronic Rheumatism. All of the eight cases considered in this class were such as had suffered, for a considerable time, recurrent or progressive heart disease associated with acute rheumatic fever. The majority had died of broken cardiac compensation. The most constant cardiac finding was a chronic interstitial myocarditis, while an old endocarditis involving one or other of the valves was not uncommon. In this series of cases the lesions of the aorta and of the smaller coronary arteries was quite constant, but varied in the extent of the reaction. Macroscopically the intima was more or less nodular. At times the thickening of the intima was quite extensive, while, however, it showed little evidence of degeneration or atheromatous change. There was usually a great loss in the elasticity of the entire vessel wall, and the artery felt thicker and heavier.

Sections of the aorta showed that the thickened intima consisted mainly of a hyaline looking fibrous tissue, in which numerous fine elastic fibers were seen. The media appeared compact and dense, and the muscle cells did not appear as frequent as usual. The vasa vasorum were seen commonly in the middle third of the media, and some were found in the inner third. The majority of these vessels had their direction parallel to the elastic fibers and a considerable number were surrounded by a fibrous tissue, which had replaced the muscle cells and interrupted the concentric layers of elastic fibers. A slight lymphocytic infiltration surrounded many of them, and plasma cells were also present. Polymorphonuclear leukocytes were not present. In the adventitia there was a fairly dense stroma of connective tissue built closely upon the outer border of the media, so that the thickness of the entire wall was increased. The small bloodvessels were not congested, but in their vicinity there were some scattered lymphocytes. The vasa vasorum in the adventitia had thickened walls.

The changes observed in the vicinity of the coronary arteries of the heart are those with which we are all familiar in chronic interstitial myocarditis. In fact, these very interstitial myocardial changes which have attracted our attention are the result of non-suppurative processes occurring in the neighborhood of the finer coronary arteries. Thus the pathological process about the arteries in the late stages of rheumatic fever is one of inflammatory fibrosis. This fibrosis is particularly evident in the first part of the aorta and about the smaller branches of the coronary artery of the heart.

Discussion. There appears to be a fairly definite form of arterial disease which is associated with rheumatic fever in its different stages. The arteries react to the irritant in a true inflammation and this reaction is to be observed in the adventitia and the outer portion of the media. In the acute stages the inflammatory exudate is of the non-suppurative variety in which the lymphoid cell is most prominent. The inflammation occurs particularly in the neighborhood of the smaller arteries, while the medium-sized vessels are little affected. On the other hand, the larger arteries, which are supplied in their outer coats by nutrient vessels, are damaged by the inflammatory process which travels along the vasa vasorum.

During the acute process the fixed tissues in the immediate neighborhood of the small arterioles are damaged or even destroyed, but abscesses are not formed. In the aorta the destruction of tissue is particularly noted in the loss of muscle and elastic elements. Similar degenerations are common in the heart. At times the degenerative processes are quite extensive, leading to the loss of considerable tissue of the part, and probably weakening the media. The intima of the arteries does not appear to be primarily affected. In the early stages a slight superficial fatty change is sometimes noted, while later, in the chronic stages, the intima proliferates, giving rise to a nodular endarteritis.

The repair, following the inflammatory process of the media and adventitia of the arteries, is by fibrous tissue. Thus the aorta in chronic rheumatism is disturbed by a patchy fibrosis, better spoken of as chronic productive mesaortitis. It is evident that the arteries which are involved in a chronic mesarteritis have lost much of their elasticity and may become subject to a diffuse dilatation of their lumen.

In some respects the acute stage of the mesarteritis resembles the early process of syphilis, but with this difference, that the destruction of the tissues in syphilitic mesarteritis has other qualities, in that the lymphoid infiltration about the vasa vasorum is greater, gummy necroses are often seen, and granulomatous tissue surrounds the areas of greatest reaction. The invasion of the capillaries through the media toward and into the intima is more marked in syphilis, while the nodular endarteritis is also far more decided.

In 1903 Chiari suggested the division of productive mesaortitis (as well as mesarteritis) into two groups, type "A" and type "B" respectively. His type "A" is a chronic inflammatory disease of the media secondary to an intimal process. The mesarteritis type "B" is a primary inflammatory process involving the media, which is usually of infectious origin and most commonly due to syphilis.

As I have on a previous occasion pointed out, Chiari's classification is a good one, but it must always be borne in mind that this type "B" (productive mesaortitis) must include other infectious inflammatory conditions of the media than syphilis. As has been indicated above, the lesions occurring in the arteries in rheumatic fever belong to the group of productive mesarteritis type "B."

UNILATERAL SCLEROSIS OF THE PULMONARY ARTERY.

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(From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.)

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UNILATERAL SCLEROSIS OF THE PULMONARY ARTERY.

By Frank A. Evans.

(From the Pathological Laboratories, University of Pittsburgh, Pittsburgh, Pa.)

[284] These studies were undertaken upon the presentation of a particularly interesting case, which showed an advanced unilateral sclerosis of the pulmonary artery associated with a condition of collapse and fibrosis of the opposite lung. This remarkable association, with such a striking difference in the character of the vessels of the two lungs, offered an excellent opportunity to investigate the pathological process which had occurred in the arteries and to associate these changes with the altered conditions in the pulmonary circulation.

It is rather infrequent in the human subject to have an opportunity of studying semi-experimental circulatory disturbances having pathological changes in the arteries as their sequel. Here, however, in a paired organ there was demonstrated a process by which the circulation had been profoundly altered in the one and which had secondarily led to circulatory changes (it may be increased pressure) in the arterial tree of its fellow organ.

The presence of small isolated nodules upon the surface of the pulmonary arteries has been repeatedly commented upon and these lesions are not uncommonly found, when properly searched for, in individuals above middle age. These nodular elevations, which present a yellow appearance, are seen at the points of bifurcation of the pulmonary arteries, as well as along the main stem. There appears to be no difference in their distribution in the two lungs, nor does it appear that any one lobe is affected more than another. These small plaques in the pulmonary vessels seem to bear no relation to

[284] changes occurring in the systemic arteries. At times, however, these sporadically distributed nodules are more extensive, showing actually atheroma and calcification, and, as in the case of Ruppert, leading to a narrowing in some of the branches. Somewhat similar cases are reported by White, Kidd, McPhedran, and Mackenzie. On the other hand, Thorel believes that the pulmonary scleroses differ essentially from those occurring in the aorta and that they are rather of a character of medial sclerosis due to calcium metastasis. Several cases have been described in which this condition of medial degeneration with but little intimal sclerosis has been the main finding.

It would appear, however, that as the arteries of the lesser circulation differ in no essential way from the systemic vessels and the influences brought to bear upon them are, in many respects, similar, the lesions occurring in them are comparable. This view is taken by Torhorst and Ehlers. To these we will refer again.

We have undertaken the histological examination of the pulmonary arteries of the case in question and have further compared the lesions observed in it with the nodular variety which is more commonly encountered in elderly persons.

Before entering upon the essential points in these pathological processes it is necessary to briefly indicate the histology of the pulmonary artery. The structure of these vessels we have found to compare closely with the description given by Torhorst, and his anatomical arrangements will be used as the basis upon which the arteriosclerotic changes are discussed in this paper.

The normal structure of the pulmonary artery and its main branches simulates very closely the architecture of the aorta. The outermost coat is represented by an adventitia consisting of a loosely arranged fibrous tissue interspersed by some elastic
[285] fibers and having occasional longitudinal bundles of muscle fibers scattered through it. Nutrient vessels of different sizes course through its loose connective tissue. Closely applied to its inner border is the media characterized by many strong elastic fibers, circularly disposed, and between them are muscle cells set at all angles, but principally having a circular

direction. Along the inner border of this laminated coat is [285] the musculo-elastic layer running longitudinally to the vessel, but whose individual muscle bundles crossing each other at acute angles form a net work. This musculo-elastic layer also contains elastic fibers, which along its inner border are aggregated into a denser bundle to form the inner boundary between this layer and the intima proper. The intima which is the innermost layer has, in the main, a circular direction and is made up of connective tissue, but is rich in fine elastic fibrils often giving the appearance of strong elastic tissue fibers. In the small arteries both the musculo-elastic and connective tissue layers are thin and weak.

Although our study deals more particularly with the changes in the pulmonary artery, we have added some of the history as well as a detailed description of the lungs, so that the points bearing upon the etiology of the pathological processes may be appreciated.

Mrs. X, age 39. The patient's family and previous history were negative. She claimed to have been well until a year ago. She was married and had nine children, three of whom died in infancy. She had one miscarriage of twins seven months old, just before the onset of her present illness, and has not menstruated since. She has always worked hard and her habits of life have been good; she denied lues.

Her present illness began with the miscarriage, for upon getting up after this confinement, December 25, 1909, she noticed her feet and ankles were swollen. This condition progressed and in three days her feet and legs were excessively swollen as far as the knees, so that she thought they would burst. Then the abdomen began to swell and at the end of a week " was filled as tight as a drum." She then went to a hospital, where she remained for five weeks, with no benefit, except that the swelling of her feet and ankles somewhat subsided. This œdema returned as soon as she got up, and she again returned to the hospital for two weeks, and later again for six weeks, but did not improve. Since June 3, 1910, she has been at home. Ever since the miscarriage she has been cyanotic, especially about the face, and worse when she was on her feet. About three months previous to exitus she began to be troubled with pain and soreness in the liver region and entered the Mercy Hospital. These symptoms were severe and for the last three weeks of her life she suffered continuously. No history was obtained of a previous acute intrathoracic lesion.

Autopsy.—No. 60, November 27, 1910. Dr. S. R. Haythorn.

[285] The body was that of a well-developed woman, 146 cm. tall. The tissues of the face, ears, lips and extremities had a purplish-blue appearance as of venous congestion. The scleræ were slightly jaundiced. Large distended veins were present over the lower portion of the abdomen, as well as on the lower extremities. There was an œdema of the lower abdomen and extremities.

In the thorax extensive adhesions were found in the right pleural cavity, almost completely obliterating it. The right lung was very small and was crowded towards the vertebral border, and was firmly held in this position by the adhesions. The left pleura was free and the lung appeared of more than normal size. The pericardium contained over 300 cc. of a clear fluid.

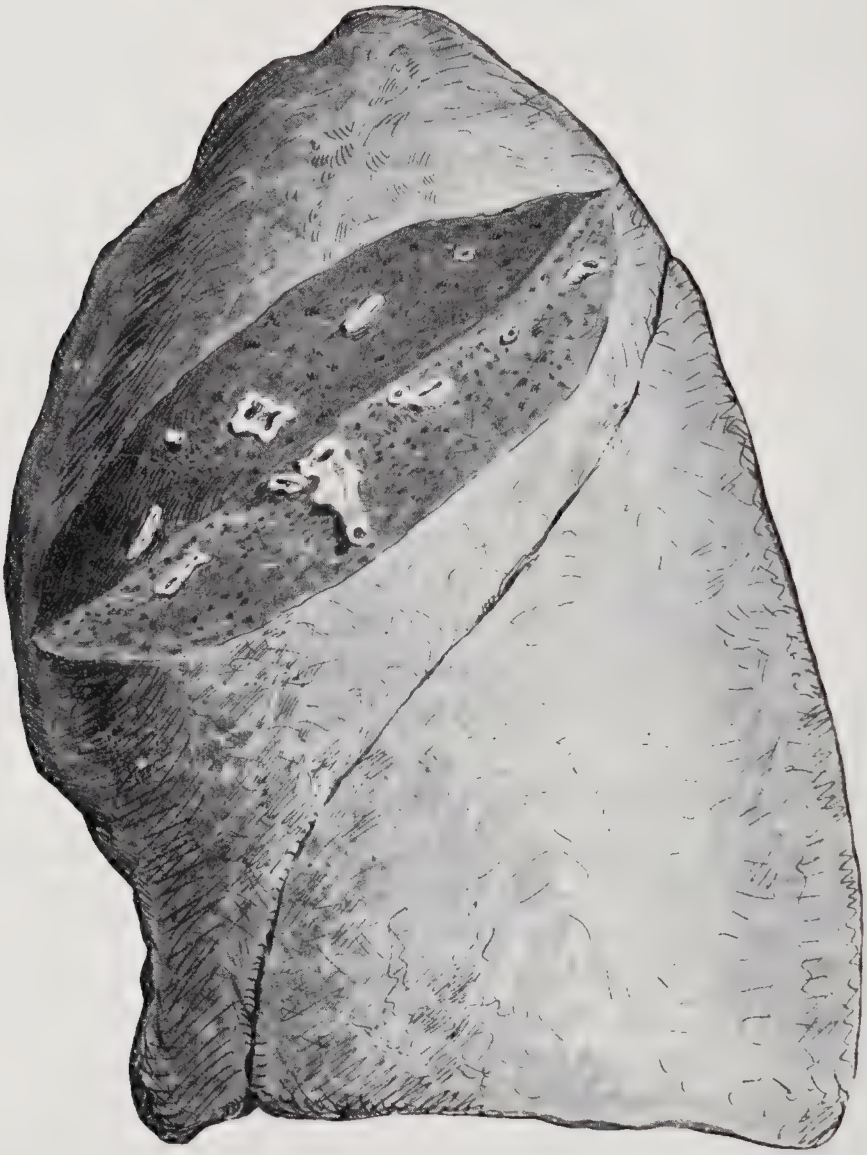


Fig. 1.—Left lung, showing marked sclerosis of pulmonary arteries.

Heart: Weight 385 gm. Over the right auricle and ventricle were several milk spots, the largest being 1.5 cm. in diameter. The right auricle was much dilated, and the right auricular appendix contained a laminated red and gray clot. The coronary sinus appeared to be dilated at its mouth. The cavity of the right ventricle was large and the muscular wall appeared quite thick (12 mm.). The papillary muscles in the right ventricle looked like those of the left heart. The whole structure of the right heart was hypertrophied. The tricuspid and pulmonary valves were all thin and leaf-like, showing no evidence of sclerosis. The base of the pulmonary artery showed some diffuse and nodular thickening of the intima, with some areas showing deep fatty change. The left heart was well contracted and the cavities were empty. Both auricle and ventricle appeared of the usual size and showed no definite change. The mitral valve was a little grayish and slightly thickened. The aortic leaflets appeared healthy. The base of the aorta showed a few small nodules of sclerosis close to the openings of the coronary arteries. The coronary arteries showed no evidence of sclerosis. The foramen ovale was patent. The arteries of the systemic system showed only occasional and slight sclerosis at the points of bifurcation. [285]

Left Lung: The organ was diffusely enlarged and appeared overdistended. It was free from adhesions and the outer surface was marbled by a considerable deposit of coal pigment. Over the pleura were a considerable number of white and well-defined lines following the course of the lymphatic channels. The organ crepitated throughout. There was no evidence of consolidation or of tuberculosis. The cut surface of the lung presented a very remarkable appearance, in that the blood vessels in both lobes stood out very prominently, giving them, at first sight, the appearance of bronchi. The main trunk of the left pulmonary artery was irregularly thickened and the intima was quite nodular. The thickening, though nodular, was diffuse and affected the circumference of each vessel. Many of the vessels were of cartilaginous hardness. In places the lumen of the artery was distinctly narrowed, while in other places small pouches occurred in the course of the vessel and particularly at the points close to a bifurcation.

Right Lung: The surface of the organ was covered by extensive old adhesions. The organ was very small and collapsed and formed a little shrunken mass lying in the upper and inner part of the chest cavity. This lung was meaty in character, and contained but little air. The tissues were, in part, firm and somewhat fibrosed. There was no evidence of tuberculosis. The bronchi were small and quite pale. The pulmonary arteries were thin-walled and no evidence of sclerosis could be observed in any of them. The lung on section showed no evidence of consolidation, but the lung tissue was tough and almost airless. There was a fair amount of anthracotic marbling through this organ. [286]

In the remaining parts of the body no important findings were made other than the presence of a considerable ascites and a con-

[286] gestion of the veins in the abdomen and extremities. No evidence of any chronic infective process or of syphilis was obtained.

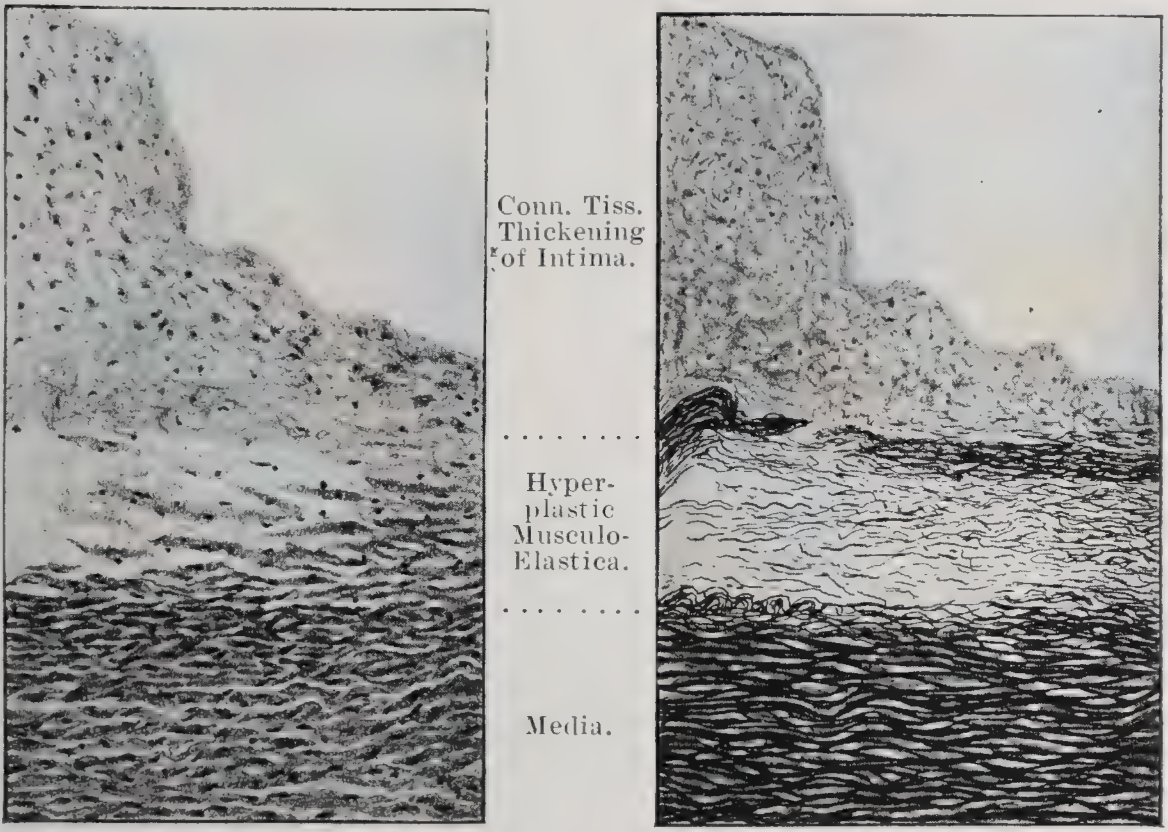
The microscopical examination of the right lung showed a condition of collapse of the alveoli, with a thickening of the alveolar walls. The lining cells of the air sacs were prominent and frequently were of a cuboidal nature. A considerable number of desquamated cells were present within the alveoli. Besides a general thickening of the alveolar walls, small patches of fibrosis were found scattered through the lung tissue. The vessels showed a fair amount of carbon pigment surrounding them, but their walls were unchanged. There was no evidence of old or recent inflammatory reaction within the essential tissues of the arteries, although some of them showed fibrosis of the stroma in which they rested. Here and there this fibrous tissue contained small collections of lymphocytes. Nodular endarteritis was entirely lacking in the vessels of this lung.

In the left lung the alveoli were large and distended. They were, in the main, free from exudate, save some small collections of leucocytes close to some small bronchi. The alveolar walls were quite thin. The striking feature throughout the structure of this lung was the extensive and irregular nodular thickening of the arteries. This thickening was not accompanied by any change in the lung tissue immediately surrounding the arteries, although the large vessels were accompanied by a fair amount of fibrous tissue and anthracosis. The thickening was confined to a reaction in the intima, the media and adventitia remaining undisturbed as far as the microscopical examination could determine.

The remarkable unilateral sclerosis of the pulmonary artery associated with collapse and fibrosis of the lung on the opposite side, as well as with a decided hypertrophy of the right heart, led us to study more minutely the changes in the pulmonary arteries. As has been above described, the thickening of the pulmonary arteries was diffuse and nodular, and macroscopically it appeared that the nodular change was only a more intense and localized condition of the diffuse intimal sclerosis. Portions of the pulmonary artery were selected from different areas in the left lung so that the histological characters of the sclerosis might be studied in all its phases.

Microscopical Examination of Pulmonary Artery.

Main Branches: The microscopical examination of the pulmonary arteries immediately revealed the fact that an important change had occurred in the intima. In the areas where the thickening was of a diffuse nature the media and adventitia were quite loose and devoid of any evidence of inflammatory infiltration. The [286] nutrient vessels were not increased in number, but many of them showed some narrowing of their lumen. The outer two-thirds of the media was regularly disposed with alternating layers of elastic fibers and muscle cells. On the other hand, the inner layer of the media was somewhat changed through the loss of muscle fibers and the more close packing together of the elastic strands. In this situation the areas previously occupied by the muscle cells now showed the presence of granules of a fatty nature. Thus with the sudan stain a narrow layer of fatty degeneration affecting the muscle fibers of the innermost zone of the media was easily demonstrated, and the reaction and degeneration were more evident here than in the diffusely-thickened tissues of the intima. This, however, was not the case where the intima showed nodular thickening, in which the extensive degenerations were found in the deep portion of the intima.


Conn. Tiss. Thickening of Intima.
Hyper-plastic Musculo-Elastica.
Media.

Hematoxylin and Eosin.

Verhoeff's elastic tissue stain and Eosin.

Fig. 2.—Sclerosis of pulmonary artery, showing hypertrophy of musculo-elastic layer and hyperplasia of connective-tissue layer of intima.

The internal elastic lamina was, for the most part, broken up into a multitude of fine fibrils. Intermingled with these elastic fibers was a varying amount of muscle tissue having a longitudinal direction. For the most part, there was some increase in the quan-

[286] tity of the muscle tissue in this layer. More or less fatty degeneration was also present in these muscle cells, but where the intima was only moderately and diffusely thickened the amount of fatty change was not great.

The diffuse thickening of the intima proper was mainly the result of a hyperplasia of the connective tissues and elastic fibrils lying between the endothelium and musculo-elastic layer. Nevertheless, occasional strands or small bundles of muscle tissue were found to extend into this layer from the deeper musculo-elastic lamina. The connective tissue thickening consisted of a compact layer in which the connective tissue cells were longitudinally disposed, and, in places, were quite regularly arranged in layers. In other places, again, this connective tissue appeared looser and the cells had a more stellate appearance. The matrix in which the connective tissue cells rested was hyaline in appearance, which sometimes took on an œdematous character.

The nodular thickening of the arteries was a process lying entirely on the inner side of the internal elastic lamina, in which a reaction of both proliferation and degeneration was evident. The proliferative change consisted chiefly in a thickening of the connective tissue beneath the endothelium, in which relatively few elastic fibers were to be found. This hyperplasia was made up of spindle-shaped cells which were arranged more or less loosely and in a parallel manner. Where the tissue was less compact the cells had stellate characters. Near the surface this newly developed connective tissue was well retained and showed no evidence of degeneration. Close, however, to the boundary between intima and [287] media, extensive fatty change involved the various elements including the muscle and elastic fibers of the immediate vicinity. This process of degeneration was not alone to be observed in the intima, but extended into the media for a short distance. Thus in the vicinity of the musculo-elastic layer no definite structure could be made out, but there atheroma was involving the several tissues. For the most part these nodular areas were similar, but it was observed that some of them gave distinct evidence of inflammatory cells, mainly lymphocytes, scattered through them. It was also observed that the adventitia opposite these nodular areas showed some slight inflammatory reaction in the vicinity of the vasa vasorum. Furthermore, where the nodular thickening of the intima was extensive, the media was thinner than in the remaining portion of the vessel wall.

Small Branches: In examining the lung tissue, extensively sclerosed arteries and arterioles of small size are encountered. In fact, throughout the lung tissue, wherever small arteries are met with, sclerosis of their structure is found. This sclerosis simulates in every respect the changes observed in the larger arteries. The lesion is for the most part confined to the intima and is of proportionately greater extent than in the large vessels. The lumen is greatly reduced and the architecture of the internal layer much altered. The adventitia and media show relatively little change save that here and there a slight amount of inflammatory infiltration can be seen near the nutrient vessels. On the other hand, the internal elastic lamina and all that lies within it are much altered. The internal elastic lamina commonly shows a splitting into multiple layers, but there is no evidence of any extensive formation of elastic fibrils on the tissue of the greatly thickened intima. There is a thick layer of connective tissue between the musculo-elastic layer and the lumen. The amount of this connective tissue varies in each vessel, as well as on different sides of the same artery. In every instance much atheroma is found in the deep portion of the newly formed tissue, and this fatty change of the intima has also extended into a portion of the media. Inflammatory cells, mainly of the nature of lymphocytes, associated with a few polymorphonuclear leucocytes and plasma cells, are also seen. The musculo-elastic

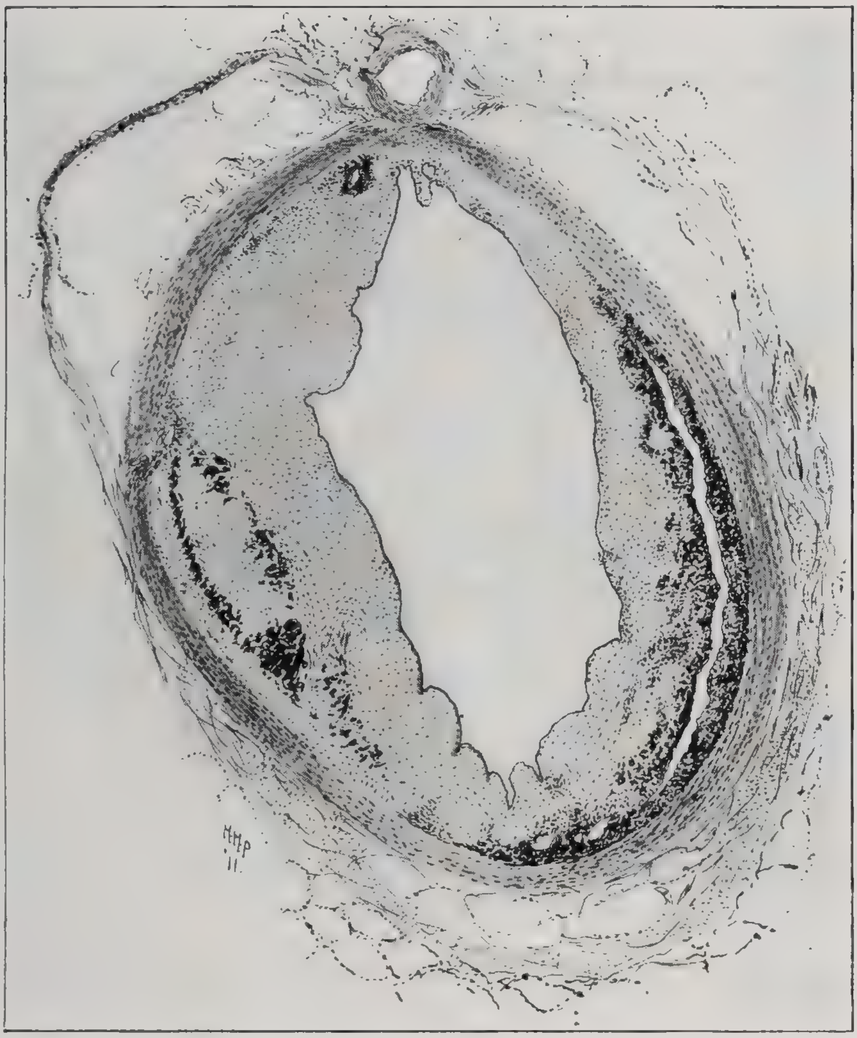


FIG. 3.—Sclerosis of branch of pulmonary artery, showing intimal thickening with deep fatty degeneration.

[287] layer shows an irregular amount of hypertrophy, as well as evidence of degeneration. The hypertrophy of this layer does, however, not make up for much of the wide spread thickening observed throughout the arteries. This hypertrophy of the musculo-elastic layer is not uniform and, in places, is wanting.

Arteries of Right Lung: Sections made of the various arteries in this organ showed a normal structure to be present in all of them. Only very occasionally in some of the large branches were some microscopic evidences of an increase in the connective tissue layer of the intima observed. The media and the adventitia appeared normal, there being no evidence of inflammation or sclerosis. No evidence of degeneration was evident in any portion of the pulmonary artery of the right lung.

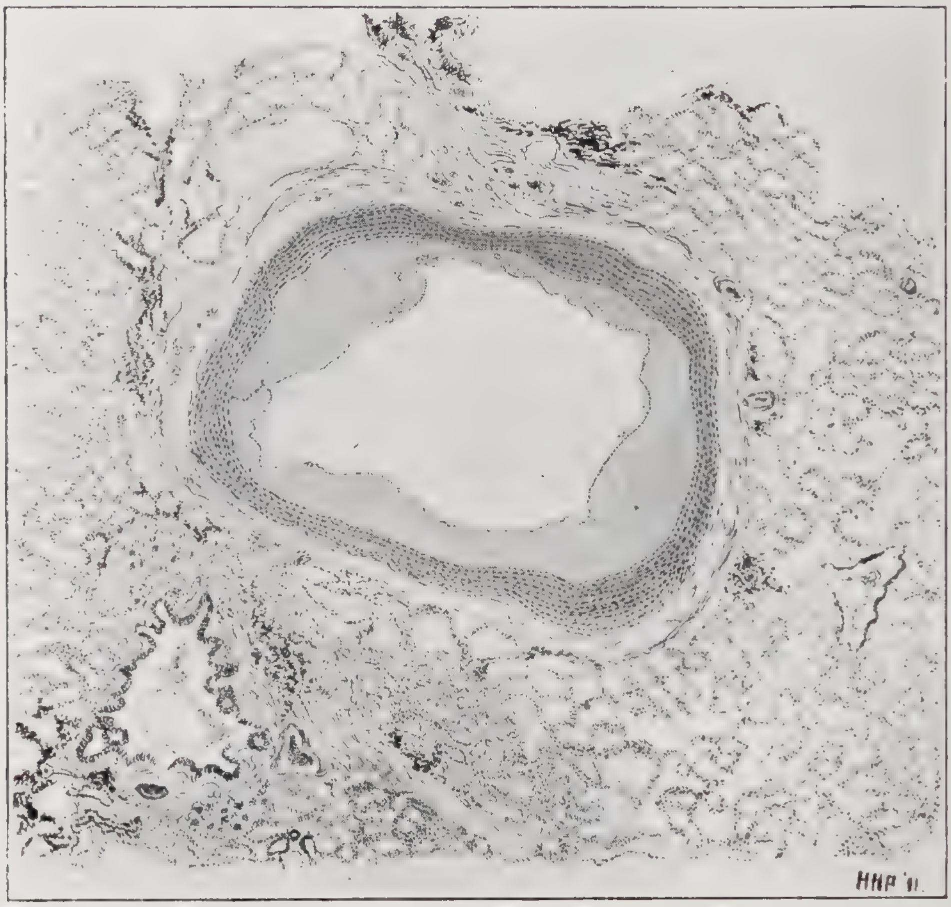


Fig. 4.—Sclerosis of small branch of pulmonary artery.

To resume, the case was one of a woman, aged 39, who died with symptoms of failure of the right heart, with chronic passive congestion, ascites and œdema, in less than a year after a twin pregnancy, which ended in a miscarriage at the seventh month. In addition to the clinical findings, the autopsy revealed a hypertrophied right ventricle and a completely collapsed right lung with firm old pleural adhesions rendering this lung almost, if not completely, incapable of functioning. [287] The left lung showed some compensatory emphysema and an arteriosclerosis of the pulmonary arteries, which was distributed throughout both lobes. The extensive arteriosclerosis began at the left pulmonary artery and was distributed as a diffuse and nodular disease throughout its branches. The disease was one of the intima in which hypertrophy of the musculo-elastic layer was commonly found, while an extensive connective tissue proliferation underneath the endothelium had led to much irregular distortion and narrowing of the lumen. The hypertrophy in these tissues was followed by a considerable fatty degeneration which involved the tissues of the intima and sometimes attacked the neighboring media. The elastic tissue showed little evidence of proliferation, but the internal elastic lamina was broken up into multiple strands. The narrowing of the lumen was in some instances very extensive, and simulated the sclerotic condition of the arteries of the systemic tree, showing endarteritis chronica deformans. Not uncom- [288] monly the process of hypertrophy of the musculo-elastic layer, hyperplasia of the sub-endothelial connective tissue and extensive fatty degeneration were to be observed in the same specimen. None of the vessels showed lesions which simulated syphilis.

In view of the absence of syphilis in any part of the body, as well as evidence of any definite infective process to which the unilateral arteriosclerosis could be ascribed, the actual condition found in the respiratory system is worthy of close consideration. We have evidence in the hypertrophy of the right heart of an increase in the resistance of the blood flow through the lesser circulation and in explanation of this we have the presence of an almost completely collapsed right lung of some time standing. The presence of fibrosis within this organ, as well as the firm bands of connective tissue which bound it down, were instrumental in impeding the blood flow through this lung. It is interesting to note that with the diminishing circulation in this organ no reaction of the nature of compensatory hypertrophy of the intima of the pulmonary arteries of the right side, as would be expected from the theory of Thoma, was found. Here we had every condition making

[288] for a slowing of the blood stream and for a disproportion between the blood content and the vessels' walls, and yet no definite organic change developed. On the other hand, the left lung responded in a compensatory emphysema to the respiratory incompetence of the organ on the right side. Moreover, the pulmonary circulation was very much disturbed by the collapse of the right lung, so that a greater amount of blood was required to pass through this one organ. It is probable, although this is not entirely proved in this case, that the blood pressure in the right pulmonary circulation was increased. The hypertrophy of the right heart is an evidence of this. This increased blood pressure was mainly borne by the vessels of the lung, which was functioning in an excessive degree.

For comparison we have examined five other cases in which minor scleroses, usually of the nature of isolated plaques, were found irregularly scattered through the main arteries. In two of the cases the arterial changes consisted of a connective tissue thickening of the superficial intima without showing any evidence of proliferation in the musculo-elastic layer, or any sign of degeneration. The findings in these vessels appeared to be only incidental to the cause of death and the post mortem findings. In the three other cases not only was a connective tissue proliferation observed along the inner border of the intima, but in each there was found an hypertrophy of musculo-elastic layer, with more or less evidence of degeneration in this tissue. These latter cases were associated respectively with (1) heart, kidney, and arterial disease, (2) recurrent heart disease, and (3) chronic heart disease with gonorrhœal polyarthritis. It would appear that, when circulatory disturbances are such that an alteration in the blood pressure of the pulmonary system is brought about, an hypertrophy of the musculo-elastic layer is an early response to this change. On the other hand, nodular thickenings may also occur in the pulmonary system simulating the chronic endoarteritis of Virchow. It would thus appear that the pulmonary arteries respond in a manner quite similar to the arteries of the systemic circulation.

Both Torhorst and Ehlers concluded that degenerative changes in the pulmonary artery begin in the musculo-elastic [288] layer, simulating the reaction which Jores described for the aorta. Just as Jores indicated the development of two different types of reaction, the "hyperplastic intimal thickening," involving the musculo-elastic layer and the inner elastic lamella, and the "regenerative connective tissue increase of the intima," originating in the innermost layer, so have all investigators of the scleroses of the pulmonary arteries described reactions of a like kind. Ehlers' studies on pulmonary arteriosclerosis led him to conclusions in agreement with those of Jores, namely, that the connective tissue thickening of the intima commonly followed upon a primary degeneration of this hyperplastic musculo-elastic layer. This, on the other hand, Torhorst did not find, but he believed that the connective tissue thickening of the intima which brings with it a rich supply of fine elastic tissue was primary and together with the hyperplasia of the musculo-elastic layer formed the reaction in response to the increase in blood pressure. These two types of reaction, or according to some, these two stages of the same reaction, which resemble very much those reactions of the aorta named by Jores, "hyperplastic intimal thickening," and "connective tissue increase of the intima," are processes which take place in two different layers, normally seen in the large arteries of the lesser circulation. The first type, which corresponds to the "hyperplastic intimal thickening," consists of an hypertrophy of the musculo-elastic layer, or the "longitudinal layer" of Ehlers, with a change in the internal elastic lamella. The muscular elements increase and the elastic tissue becomes more abundant, and by the crowding together of the elastic tissue fibrils the appearance of newly developed strong fibers becomes marked. This may occur without any involvement of the internal elastic lamina, but usually the hypertrophy of the muscular elements results in a splitting of the strong elastic fibers, with the result that more fine ones come to view, giving the appearance of an equal amount of elastic tissue, spread over a greater area. The second type of sclerosis, which corresponds to the "connective tissue increase of the intima," consists of an increase of the innermost connective tissue layer of the intima.

[288] This layer may become thicker as a result of the proliferation of sub-endothelial connective tissue and may or may not be rich in fine elastic tissue fibrils. The connective tissue may increase out of proportion to the elastic tissue and result in a considerable intimal thickening, comparatively poor in elastic tissue fibrils, or even free from them along the inner edge. On the other hand, the elastic tissue of the innermost layer may increase to an unusual extent, resulting in the crowding together of the fine fibrils and giving the appearance of stronger ones in a comparatively thin margin of tissue. Fatty degeneration, though undoubtedly starting in the musculo-elastic layer and probably in the muscle cells or the new formed connective tissue, may spread both inward and outward and involve both intima and media. Later the intima
[289] may show a type of hyaline degeneration and this without much thickening.

In view of these observations the question arises whether one can definitely determine whether the thickening of the innermost layer of connective and elastic tissue or the hypertrophy of the musculo-elastic layer was primary to the degeneration, as observed in our case of blood pressure sclerosis of the pulmonary arteries. The microscopical study showed both types of change to be present, the hypertrophy of the musculo-elastica, with splitting of the fibers of the internal elastic lamina, being the most striking. However, in most of the areas of degeneration there was a great excess of connective tissue in the overlying layer, and it was shown that the nodular eminences observed macroscopically were due to this thickening of the innermost layer.

To sum up, all the cases studied showed plaques on the pulmonary arteries having a gross appearance more or less resembling each other, but differing slightly in color and extent of distribution. In our first case were observed conditions which indicated increased blood pressure as a possible etiological factor, but in all the others no definite etiology could be assigned, and they are probably examples of the common types of arteriosclerosis of the pulmonary arteries, associated with some general arterial or other changes as a result of systemic processes. In both the former and the latter the type seen in

the pulmonary arteries was comparable to the "hyperplastic [289]
intimal thickening," and of the type related to the "regenerative connective tissue increase of the intima," as described by Jores for the aorta.

As the intimal changes in our principal case were so advanced, it is impossible to say which of the proliferative reactions was primary. In none of the vessels was a pure form of proliferation of either the superficial or deep intimal layer to be found. It was, however, evident that the process of degeneration began in the hypertrophied musculo-elastic layer and from here extended into the connective tissue thickening, as well as into the media. Nevertheless, it is quite possible that the presence of the deep degeneration in the intima acted as a stimulus calling forth a still further proliferation in the overlying connective tissue. We believe, however, that, like the reaction in the systemic arteries, the hypertrophy of the musculo-elastic layer was the result of the abnormal circulation in the one lung following upon an impeded circulation on the opposite side. The process of degeneration was secondary to the proliferative reaction.

In conclusion, I wish to express my appreciation of the privileges I have enjoyed at the Pathological Laboratory of the University of Pittsburgh, and to thank Dr. Oskar Klotz for the many courtesies I have received.

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The Medical Profession, Public Opinion and Animal Experimentation.

By OSKAR KLOTZ, M.D.,
Pittsburgh.

(Read at the General Meeting of the Medical Society of the State of Pennsylvania, Scranton Session, September 25, 1912.)

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e Medical Profession, Public Opinion and Animal Experimentation.*

By OSKAR KLOTZ, M.D.,
Pittsburgh.

nswer to the invitation of the state l society to discuss this important I have been urged to accept by one ration. Briefly, this is for the full- erstanding and exposition of the n of the medical profession to the as well as the present-day attitude physician and laboratory worker to opinion upon questions mainly l.

not an infrequent occurrence that opinions are offered by each and ne upon questions which are foreign individual profession. To a cer- tent our aptitude to form these pinions is dependent upon our close tion with the not unbiased opinion daily papers. Politically, without ion we rely for our information upon the daily press and periodi- We have little time, even if we were ned, to enter into a serious research in the truth upon each clause in the m of a political party. And yet re matters of our daily life. We erested in politics because of their ssociation to our own interests and me. In such matters it would ap- hat every one, who remained even a slight extent in touch with his urroundings, should be fairly well ed to discuss the politics of the gov- t and the value of long delibera- y our political representatives. It is not, however, until we have placed ourselves in the position of one who gives initiative for new acts or one who must for his livelihood closely study a particular trade or profession, that we appreciate even in the smallest way the intricate problems which confront that particular work.

It is probably true that in none of the sciences does the individual student or critic require to be armed with such diverse knowledge and experience to have a proper understanding of his subject as in medicine. There is a long history indicating the evolution of medicine and its allied sciences. Much of what has occurred in the past influences us but little in our present position, but nevertheless the art and science of medicine has accepted much from the older teachings, particularly in placing the profession above the quality of a trade and by imbuing each of its associates with the seriousness of the work undertaken and the necessity of truthful observations for advance.

It is impossible for anyone to indicate the quality of the mind which has led the profession on the up-hill climb to the position which it occupies to-day. The character of medical thought and persuasion is the composite aggregation of experiences gathered by generations from many fields.

It has for example been through long years of observation and research that certain social laws for the prevention of smallpox have been established. These observa-

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the Pathological Laboratories, University of h.

tions were not made haphazard nor were they evolved upon antecedent theories, for the theory only followed the actual observation. At present it is not our point to discuss the value of vaccination, yet there are individuals who, without experience, either in subjects of immunity, health or disease, attack the findings of students in this work. We can not too strongly denounce such an attitude. We would offer the same criticism to each one in the professional world who, inexperienced, deemed it his privilege to offer the last word in a foreign field. For the last fifty years the medical profession has been unusually active in determining causes of disease and indicating the prevention thereof. Much of the knowledge which has been acquired through hard work is looked upon by some as the natural course of events which would have become the property of the public even though the medical profession had not existed. Of course a discussion, with such opinions, is futile and leads to no end. I would even say that many of us in our own profession do not realize and impose sufficient weight upon the difficulties which had to be overcome to reach the status of the profession to-day. The martyrs in medicine are legion, but it would be ungrateful for me to offer their names in a discussion which to some still remained unconvincing.

What I wish to emphasize to-day is that we in the medical profession must come to a closer understanding with the public. In years gone by there was a time when the physicians and surgeons were a class who stood quite apart from all other people. In the mysteries of ignorance which surrounded medicine at that time, and it is not so long ago, there was reason for maintaining a certain secrecy upon individual opinion and methods of treatment. However, as new light was shed upon the dark places the public became interested and themselves enthused in the progress made by their students. Not only did th
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istrated the truth of his researches eneral sentiment acknowledged their work. However, as the value of researches became known and as the r of men who were willing to sacri- eir time in these researches in- l, then did the people recognize and r medical investigation. It is quite that this should be as it was; name- t the benefits of the individual re- s should be definitely proved before ner demand was made for increased es for work. But the brief period has elapsed in which the untrained has permitted itself to become r with research, some demanding a e of study, has been insufficient to a proper appreciation of this work e public should not demand so much hamper in any way the progress of gations already begun. Unfor- ly such has been the attitude of vho, I fear, fall into the category of uninformed.''

ould seem superfluous to discuss the of certain animal experiments that rried on for the purpose of throwing ght upon old diseases, or that are r the purpose of making a diagnosis ividual cases. This subject is so rn that I fear much that I will say is a mere reiteration of a story as ofttimes been repeated. Particu- s this true as the medical profession recent years, had seriously to dis- nd to advance arguments to illus- heir sincerity in the value of these ments and in the benefits which they upon humanity at large.

often has this subject been discussed the term ''vivisection.'' The very ter of the word has led to many mis- tions, so that he who is smooth of can paint word pictures which will the innocent. There are probably ith us to-day who have not shuddered agraphs of description illustrating the torture of animals in days gone by, or of semireligious festivals at which animal sacrifices were offered. Even the human was in fear of the application of these cruel methods, which in ignorance and superstition were applied to one to save or soothe the ills of a more influential individual.

We are, however, to-day extremely proud that mankind, particularly through the efforts of the medical profession, has advanced beyond the stage of superstition and has a mind of the inquisitive type, wishing to know the why and wherefore of every process in nature. Instead of assuming that frame of mind, fearing to trespass on holy ground, fearing to meddle with nature's works, and even be denounced when such was done, we are willing to-day to sacrifice those conscious comforts where ''ignorance is bliss,'' to labor in untrodden fields and to uncover many of nature's mysteries. We repeat, that we are proud of the attitude assumed in medicine to-day, that she is assisting to lift the veil, particularly to disclose the dangers which have confronted human life as well as the welfare of all animals.

To-day man is the keeper of everything living; upon him depends what formerly was discussed under the survival of the fittest. Though in the wild and untamed world the survival of the fittest is dependent upon brute force as well as keenness of intrigue, to-day man in the civilized portions of the globe must bear the onus of responsibility for the preservation of life. Things are changing and many of these changes are the result of the work of man. Just as with the advance of civilization, and the development of the biological sciences there has been an enormous growth in the population of all countries, so must the very face of the world change. But with this advance man must encounter, continuously, new features which are to govern his future as well as that of everything living. It is with the knowledge of this progress in the past that every means is utilized to improve the conditions for the survival of the fittest in the future.

The advances which we to-day claim are not alone in one science, but enormous strides are being made in every science, industry and art. The eagerness for the advance of each is so great that no one science can afford to lag behind another. Scientific advances are made only by receiving assistance from ancillary subjects, and so medicine can advance only with a thorough knowledge of biology, chemistry, physics and the allied departments.

More than two thousand years ago the monarchs of India and China, fearing the plotting of their subjects, dreaded death by poisoning. Particular individuals, therefore were charged to test the foodstuffs by feeding them to animals. These were probably some of the earliest procedures in which animals were used for the determination of a certain fact. For the kings it was a legitimate procedure to which they felt nobody could object. Some centuries later more pointed experiments were undertaken to determine the character of certain vegetable poisons as well as to obtain some knowledge as to the strength with which they could be administered. However, in those ancient times too great a relation between the action of poisonous drugs and the temper of the gods was given, so that the experiments were not disclosed in the proper light. The idiosyncrasy to the action of drugs was a process of fate or due to an external influence of demons rather than to altered inherent qualities of the individual. Thus being persuaded by hallowed myths, the experimenters themselves were unable to draw proper conclusions.

And so time passed on through centuries from Hippocrates, to Galen, Avicenna and Celsus down to the seventeenth century, when a new light began to dawn in th tory of medicine. Actual observatio all matters of science were then rec and the sequence of the processes i natural phenomena were appreciated could be but a short time from the b ning of such truthful observations tha value and relation of each fact to the eral principles of the science were given proper weight. Every science, like a passes through three stages in the hi of its development. In the first stag servations are made very much at ra and without any thought of their val consequences. This in medicine is th pirical stage. Later on these fact brought together in an orderly manne the general findings are compared. uncommonly it will be found that t sults of these observations indicate a mon principle governing the process which the observations have been Then we enter upon the second Now in the ordinary course of even first and second stages are deeme many as being quite sufficient to est laws, and though this is true, in so these observers are willing to go, th secutive observations upon phen of disease, in the natural of events, are difficult to are impossible to control, and seen factors can not be properly g It is quite impossible to state how this or that factor, in a given proce played in bringing about a given Therefore, it is necessary to have means by which we can weigh each a reaction and each part of a pheno There is but one way to carry this o that is to put each factor to test.

Science has waited a long time f third stage, the stage of experimen In this, each observation which ha carefully recorded in the first stage a been assembled in the second stage to test and the weight of each ing

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often is the opinion expressed that
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cupy two distant fields. This should not be true. In fact, we welcome and admire those who are able to combine the two under the same roof. The one is but the assistant of the other and upon the second does the former place his hopes for his better work amidst humanity. Want of time is the greatest factor tending to divorce these mutual interests.

The reiteration of the benefits which mankind has obtained since the discoveries of Jenner a hundred years ago, is almost unnecessary. To recount the many applications of animal experimentation which has placed in your hand an instrument by which you are able to cope with disease would occupy a long time. Many in carrying out their missions of dealing with the sick are forgetful for the moment of the struggles by laboratory workers which made it possible for them to make a diagnosis and to carry out a successful treatment. Many of these discoveries could only have been made by the use of animal experimentation to prove the final point in the determination of the etiologic factor of disease. The character of these men who have worked and slaved in the laboratories, who have attempted, sometimes successfully, at other times without avail, to prove the *causa morbi*, can be read in the tragic histories of Reed, Lazear, Dutton, Ricketts, and others, each of whom offered his life, a sacrifice to science.

With the information that is now at hand we wonder that more did not perish in the early days of bacteriology. It is probable that over three quarters of the cases of ill health and disease which are treated by the internists are either the direct or indirect result of bacterial invasion. We well know the scorn with which Pasteur's inferences of the bacterial nature of certain diseases were received in the early sixties. We to-day would not have even this information had he not been successful, particularly with the later assistance of Koch, in reproducing the same diseases by the inoculation of pure cultures of bacteria.

The work of Ehrlich, Yersin, Kitasato, and Roux is too frequently neglected when in our daily work we are treating patients with antitoxin and other sera. The value of these need not be discussed, for if we gauge the importance of their discoveries in the terms of diphtheritic antitoxin alone, it is impossible to estimate the value in human life. There are, however, examples which are better gauged in money value. The causative agent of anthrax, black leg, swine plague, glanders, and actinomycosis was for centuries in question, and only after the proof by animal experimentation of the direct relationship of certain microörganisms to these diseases was established, has the government instituted hygienic measures, which in this country alone saves us millions of dollars annually. And all this information was received only by proof in animal experiments.

The relation of the pneumococcus to pneumonia, the meningococcus to meningitis, the *Spirochaeta pallida* to syphilis, and many other organisms to definite forms of human ills, have been and can only
be determined by reproducing the d
as demanded by Koch's third postula

In particular has bacteriology be
fertile field in which the value of a
experimentation is very patent.
pathology proper, new fields have re
been demonstrated in which the com
tive study of human diseases in
mentally produced lesions has be
greatest value. The etiological fact
nephritis have always been a sou
polemic controversy since the day
Bright. These to-day are disclosing
nature and it is probable that in
short time all will be as an open
Studies in edema and heart disease
likewise been vexed fields of disc
Here, too, we can indicate that the
edge which we do possess has be
tained by means of studying fact
fact, factor upon factor, and obtaini
actual observations where we can
them, in living tissue.

I hold no brief for the carrying
promiscuous animal experimentat
any science. It is evident, howeve
progress can only be obtained by th
onstration of truth and the truth of
tissue lies in those tissues themselve

SERUM STUDIES IN PNEUMONIA. THE ANTIGENIC PROPERTIES OF FIBRIN (EXUDATE) TO SERUM

C. C. HARTMAN

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CHICAGO

SERUM STUDIES IN PNEUMONIA.

THE ANTIGENIC PROPERTIES OF FIBRIN (EXUDATE) TO SERUM.

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The object of the work here reported was to determine, by the means at hand, the presence of antibodies in the serum of patients with pneumonia, which might assist in the removal of the fibrinous exudate during resolution. We started out on the supposition that human fibrin is more or less identical, though the possibility of its variation in diseased conditions was kept in mind.

Lamar and Meltzer[1] have reported the successful production of lobar pneumonia in dogs by intratracheal insufflation; Wollstein and Meltzer,[2] that of bronchopneumonia, noting the difference in the fibrin content of the exudate, distinguishing true lobar pneumonia from others, as well as appreciating the difference in the distribution of the inflammation, the appearance of the reaction, the resolution, and the mortality. The pneumococcus seems to call forth a reaction in the lung sufficiently characteristic to allow of its differentiation from other organisms. Lamar[3] has shown the modifying effect of the soaps on pneumococci, indicating their greater susceptibility to autolysis and to serum lysis after being acted upon by the sodium oleate. Rosenow[4] has observed the toxic qualities of pneumococci autolysates and their power to call forth antibodies. Dick[5] has shown the development of proteoclastic ferments specific for extracts of pneumococci in the blood during pneumonia. Barker[6] has shown the presence of proteoclastic enzymes in fibrinous exudates and fibrin. Opie[7] particularly has observed the proteoclastic enzymes in leukocytes, and many others have worked with different phases of immunity concerned in pneumonia.

Since fibrin is such a constant and characteristic component of the exudate in pneumococcus lobar pneumonia and distinguishes

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* Received for publication April 29, 1913.

[1] *Jour. Exper. Med.*, 1912, 15, p. 133.

[2] *Ibid.*, 1912, 16, p. 126.

[3] *Ibid.*, 1911, 13, p. 1.

[4] *Jour. Infect. Dis.*, 1911, 9, p. 190.

[5] *Ibid.*, 1912, 10, p. 282.

[6] *Jour. Exper. Med.*, 1908, 10, p. 343.

[7] *Ibid.*, 1906, 8, p. 410.

it more or less from lung exudates caused by other organisms, as well as from exudates elsewhere in the body caused by the same organism (pneumococcus), the possibility of its playing more than a mere passive part in the process occurred to us worthy of investigation; especially, since, in pneumococcus infections elsewhere, fibrin does not appear in such an abundance and in them the course is anything but analogous to that which occurs when the lung is the seat of inflammation. The situation of the infection scarcely accounts for the difference, because other infections in the lung differ in character, distribution, and course, as shown by Lamar and Meltzer, and Wollstein and Meltzer, and as has been known pathologically for a long time.

Aside from the enzymes associated with it, fibrin has been considered to be more or less an inert material, being constant in composition regardless of the location or the condition under which it arises. Its predominance in the exudate of lobar pneumonia, its purpose in the reaction, the method of its disappearance, must be explained in order fully to understand those interesting phenomena of crisis and resolution. One of the striking points in the histological picture of a consolidated lung after crisis is the beginning of melting away or digestion of the strands of fibrin just within the alveolar wall.[1] Since leukocytes contain proteoclastic enzymes, as do fibrinous exudates and blood serum, the disappearance of the fibrin would be readily explained along these lines, but it has not been demonstrated that this is actually the manner in which it disappears. Phagocytosis is considered to play little part in the disappearance of either the fibrin or pneumococci.[2] The beginning of fibrinolysis at the periphery of the alveolar plug and its appearance immediately after the crisis suggested that something might be furnished by the blood serum which aids in the destruction of the fibrin, and that this might be shown *in vitro*.

METHODS.

The fibrin was obtained by whipping specimens of blood taken from superficial veins in the arm by the use of a syringe. The fibrin mass was washed in sterile, distilled water until the hemoglobin ceased to come out. It was then placed on watch crystals, the excess water being allowed to drain off, and kept in a desiccator over potash at room temperature. One specimen, however, that from Case 7, was recovered from a clot. The fibrin, as needed, was ground to a fine powder in a mortar and suspended in a quantity of salt solution, equal to the amount of blood from which it was derived. Usually there remained enough hemoglobin attached to the fibrin to give the powder a tinge of brown. Everything was carried out with a constant view to asepsis.

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[1] Ziegler, *Pathological Anatomy*, London, 1898, p. 833.

[2] Rosenow, *Jour. Infect. Dis.*, 1911, 8, p. 500.

The experiments were based on the Bordet-Gengou phenomenon of complement fixation and patterned after the Noguchi modification of the Wassermann reaction. The fibrin suspension was used as antigen. The complement was derived from fresh guinea-pig serum and used in an amount necessary to cause complete hemolysis of 1 c.c. of a 1 per cent suspension of human cells in the presence of a standard unit of amboceptor in one hour. The red cells were, with but one or two exceptions, from a constant source.

The fibrin suspension, serum to be tested, and complement were measured out by separate, sterile, capillary pipettes and were added in the order given. All tubes were incubated either one or two hours before the addition of the amboceptor at 37° C., and were shaken thoroughly every half-hour. The final reading was taken at the end of two hours after the addition of the amboceptor.

It might be well to state that there seemed to be a greater amount of fibrin in the pneumonic blood than in corresponding quantities of normal blood (surgical cases). This impression, gleaned only from casual observation in the gross and not controlled by actual weights, is offered merely as an impression. Whether this appearance was due to a difference in the compactness of the fibrin shreds or to some other factor, we do not know. However, in view of the fact that fibrinogen is present in the serum in pneumonia in increased quantities,[1] this observation may be borne out by subsequent work.

The serum was obtained either by centrifuging the whipped blood from which the fibrin had been taken, or pipetted from blood allowed to clot. It was kept either in sterile test-tubes or sterile pipettes in a refrigerator. Thirty specimens of serum and one of pericardial fluid from pneumonia patients were used, one to four specimens being obtained from each patient. It was the intention to get specimens of serum at various periods of the disease and to try them against various specimens of fibrin. As controls, 20 specimens of serum from convalescing surgical patients were used.

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[1] Dochez, *Jour. Exper. Med.*, 1912, 16, p. 665.

ANALYSIS OF CASES.

In this series of cases, there were 21 adults, 20 males and 1 female, ranging in age from 17 to 55 years. Fifteen recovered and six died. A few of these cases were complicated by other conditions.

TABLE 1.

FIBRIN FROM NON-PNEUMONIA PATIENTS.

No.	Fibrin	Serum	Day of Disease	Termination	Lysis or Crisis	Result
1	A	Case 4	7th	Recovered	Lysis	No binding
2	A	Case 4	10th	"	"	" "
3	A	Case 4	12th	"	"	" "
4	A	Case 5	11th	Died	....	Slight binding
5	A	Normal (A)	....	.....	....	No binding
6	A	Normal (B)	....	.....	....	" "
7	A	Case 5	11th	Died	....	" "
8	A	Case 5*	15th	"	....	Complete binding
9	B	Case 7	5th	"	....	No binding
10	B	Case 6	11th	Recovered	Lysis	" "
11	B	Normal (R)	....	....	....	" "
12	B	Case 4	12th	"	Lysis	" "
13	B	Case 4	10th	"	"	" "
14	B	Normal (A)	....	....	....	" "
15	B	Normal (B)	....	....	....	" "
16	C	Case 7	5th	Died	....	" "
17	C	Case 8	9th	"	....	" "
18	C	Case 6	11th	Recovered	Lysis	" "
19	C	Normal (M)	....	....	....	" "
20	C	Normal (B)	....	....	....	" "
21	D	Case 9	?	Died	....	" "
22	D	Case 11	11th	Recovered	Lysis	Slight binding
23	D	Case 12	9th	"	"	No binding
24	D	Case 13	15th	"	"	" "
25	D	Case 7	5th	Died	....	" "
26	D	Normal (A)	....	......	....	" "
27	D	Normal (B)	....	......	....	" "
28	E	Case 14	10th	Recovered	Lysis	Slight binding
29	E	Case 15	2d	"	"	No binding
30	E	Normal (C)	....	....	....	" "

* Pericardial fluid.

Case 9 developed a terminal pneumonia on an apical tuberculosis and chronic heart disease; Case 2 was suspected of having pulmonary tuberculosis, and had a tuberculous process of the vertebrae with abscess formation. Cases 2, 4, 6, 19, 21, and 22 had a history of alcoholism. There was no definite causal relationship between the alcoholism and the pneumonia in Cases 6, 21, and 22, so that it is possible to consider 18 of the cases as true lobar pneumonia. Among the 21 cases, crisis occurred but twice (16 and 23).

The five specimens of fibrin were derived from the blood of the following patients: A, having an abscess of the thigh; B, a simple fracture; C, a minor injury; D, recovering from a herniotomy; E, having an unimportant condition.

The table represents a total of 42 trials of the five specimens of fibrin against the sera of 19 individuals, and a pericardial fluid. Thirteen of the sera and the pericardial fluid were from patients having pneumonia, and 6 from control patients. Binding of the complement was observed 4 times, with the serum (11th day) and pericardial fluid (15th day) of Case 5, with the serum of Case 11 (11th day) and with that of Case 14 (15th day). The binding of the pericardial fluid of Case 5 was complete; that of the 3 sera

TABLE 2.

FIBRIN FROM PNEUMONIA PATIENTS.

No.	Fibrin	Serum	Day of Disease	Termination	Lysis or Crisis	Result
1......	Case 1	Case 1	7th	Died	....	No binding
2......	Case 1	Case 2	13th	Recovered	Lysis	“ “
3......	Case 1	Case 2	15th	“	“	“ “
4......	Case 1	Normal	Abscess of Thigh	....	....	“ “
5......	Case 1	Case 4	7th	Recovered	Lysis	“ “
6......	Case 1	Normal (Ben)	....	....	....	“ “
7......	Case 1	Normal (O W)	....	....	....	“ “
8......	Case 1	Normal (Shupe)	....	....	....	Slight binding
9......	Case 1	Normal (Fred)	....	....	....	No binding
10......	Case 1	Normal (Mur)	....	....	....	“ “
11......	Case 2	Case 4	7th	Recovered	Lysis	“ “
12......	Case 2	Case 4	10th	“	“	“ “
13......	Case 2	Normal (Shupe)	....	....	....	Slight binding
14......	Case 2	Normal (Fred)	....	....	....	No binding
15......	Case 2	Normal (Mur)	....	....	....	“ “
16......	Case 2	Case 5	11th	Died	....	Complete binding
17......	Case 4	Case 6	11th	Recovered	Lysis	“ “
18......	Case 4	Case 5*	15th	Died	....	“ “
19......	Case 4	Case 4	12th	Recovered	Lysis	“ “
20......	Case 4	Case 4	10th	“	“	“ “
21......	Case 4	Normal (A)	....	....	....	“ “
22......	Case 4	Normal (Own)	....	....	....	Partial binding
23......	Case 4	Normal (B)	....	....	....	Complete binding
24......	Case 7	Case 7	5th	Died	....	No binding
25......	Case 7	Case 8	9th	“	....	“ “
26......	Case 7	Case 6	11th	Recovered	Lysis	“ “
27......	Case 7	Normal (M)	....	....	....	“ “
28......	Case 7	Case 7	5th	Died	....	“ “
29......	Case 7	Normal (A)	....	....	....	“ “

* Pericardial Fluid.

slight. The sera from the cases of pneumonia varied in relation to the period of the disease from the second to the fifteenth day. The temperature fell by lysis in all cases recovering; 4 patients died. The binding of complement by the pericardial fluid may be analogous to the positive Wassermann reaction obtained in the fluid of the cadaver.

The pneumonia fibrin used in these experiments was obtained from the following; Case 1, 7th day; Case 2, 13th day; Case 4, 7th day; Case 7, 5th day.

This table represents the results of 34 trials of the different specimens of fibrin against 20 sera and one pericardial fluid, 10 sera and the pericardial fluid being from cases of pneumonia and 10 sera used as controls. The pneumonia sera varied in relation to the period of the disease from the fifth to the fifteenth day. Three patients died. In those recovering the temperature fell by lysis in all.

Binding of complement occurred 10 times, 5 times by control sera and 5 by pneumonia sera. In 7 instances, binding occurred in the presence of the fibrin of Case 4.

In order to simplify technic it was decided to powder a number of specimens of fibrin, mix and suspend them in alcohol and ether (9–1) to serve as a stock supply from which amounts necessary for each day's work could be measured out. The stock suspension was made so that 1 c.c. contained an amount of fibrin equal to that derived from 5 c.c. of blood, and when diluted with 4 parts saline equaled the strength generally used in the experiments. It contained the fibrin derived from the specimens of blood from the following cases: Case 6, 11th day; Case 8, 9th day; Case 11, 11th day; Case 12, 8th day, Case 14, 9th day; Case 15, 2d day.

This mixed fibrin was used as antigen against 19 sera, 14 from pneumonia and 5 from control patients. In the 13 cases which recovered, the temperature fell by lysis in 10, by crisis in 2, and by protracted crisis in 1. The specimens of sera covered a wide range in the period of the disease—from the sixth to the twenty-sixth day. The controls included serum from a patient with known syphilis and a positive Wassermann. There was no binding whatever observed in this series.

That fatty substances are present in inflammatory processes is well known, and that lipase is present has also been indicated by Flexner.[1] The modifying effect of fatty substances upon bacteria, shown by Lamar, suggested the possibility of their having a similar effect upon fibrin. An attempt to demonstrate this was made by subjecting specimens of fibrin to the action of sodium oleate (Merck) in 1–1,000 solution over night at room temperature. The fibrin was thrown down by the centrifuge, washed once in saline, and resuspended in saline to the approximate strength used in the previous experiments.

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[1] *Jour. State Med.*, 1912, 20, p. 193.

TABLE 3.

MIXED FIBRIN—KEPT IN ALCOHOL AND ETHER.

No.	Serum	Day of Disease	Termination	Lysis or Crisis	Result
1......	Case 16	7th	Recovered	Crisis 8th day	No binding
2......	Normal (D)	....	....	....	" "
3......	Case 16	14th	Recovered	Crisis 8th day	" "
4......	Normal (E)	....	....	....	" "
5......	Case 16	18th	Recovered	Crisis 8th day	" "
6......	Case 17	7th	"	Lysis	" "
7......	Case 18	7th	"	"	" "
8......	Case 16	26th	"	Crisis 8th day	" "
9......	Case 17	15th	"	Lysis	" "
10......	Case 18	14th	"	"	" "
11......	Case 19	11th	"	"	" "
12......	Normal (F)	....	....	....	" "
13......	Case 19	24th	Recovered	Lysis	" "
14......	Case 20	7th	"	Protracted crisis	" "
15......	Case 21	7th	"	Lysis	" "
16......	Case 22	6th	Died	....	" "
17......	Normal (G)	....	....	....	" "
18......	Normal (Syphilitic (H)	....	.......:..	....	" "
19......	Case 18	4th day after crisis	Recovered	Crisis ? day	" "

TABLE 4.

SOAPED FIBRIN.

No.	Serum	Day of Disease	Termination	Lysis or Crisis	Result
1......	Case 16	7th	Recovered	Crisis 8th day	No binding
2......	Normal (D)	....	....	....	" "
3......	Case 16	7th	Recovered	Crisis 8th day	" "
4......	Case 16	14th	"	" " "	" "
5......	Case 16	18th	"	" " "	" "
6......	Case 17	6–7th	"	Lysis	" "
7......	Case 18	7th	"	"	Slight binding
8......	Normal (I)	....	....	....	No binding

The fibrin, subjected to the action of sodium oleate, was tried against 7 different sera—5 pneumonia and 2 control. All of the pneumonia patients recovered, one having a crisis. A slight binding by the serum of Case 18 was the only instance of binding observed.

Experiments were also undertaken to determine the presence of antibodies in the serum to the decomposition products of fibrin.

A weighed amount of powdered fibrin (0.05 gm.), approximately equal to the average amount derived from 5 c.c. of blood, was mixed with a suspension of fresh pus cells from an empyema in distilled water, a little chloroform added, and the whole placed in an incubator at 37° C. for 60 to 70 hours. A similar amount of fibrin was incubated for 20 hours, with pus cells from the same source, but having been preserved in 50 per cent glycerin for 2 days. After incubating, the remains of fibrin and pus cells were thrown down by the centrifuge and the supernatant liquid pipetted off. This was used as antigen in amounts of 3 to 5 drops.

TABLE 5.

PRODUCTS OF FIBRIN DIGESTION.

No.	Serum	Day of Disease	Termination	Lysis or Crisis	Result
1.......	Case 19	24th	Recovered	Lysis	No binding
2.......	Case 20	7th	"	Protracted crisis	" "
3.......	Case 21	7th	"	Lysis	" "
4.......	Case 22......	6th	Died	....	" "
5.......	Normal (G)	....	....	....	" "
6.......	Normal (H) (syphilitic)	....	....	....	" "

The products of digestion of fibrin by leukocytes were used against 6 sera—4 pneumonia and 2 control. The pneumonia sera varied in relation to the stage of the disease from the sixth to the twenty-fourth day. Binding did not occur in any instance.

If we eliminate from our various experiments all those reactions which were at all questionable, that is, where binding was not marked, there remain several definite and distinct observations which seem to be worthy of consideration.

The fibrin of Case 4, obtained about the seventh day of the disease, bound complement more or less completely with every serum, pneumonia and otherwise, against which it was tried. Some of these sera had shown no binding with several other specimens of fibrin. This makes it appear that this specimen of fibrin differed in some respects from the other fibrins against which these sera had been tried. The stage of the disease at which the fibrin was obtained was similar to that of Case 1, which did not show this reaction with any sera. Case 1 was a female who died in her illness, while Case 4 was a male who recovered. The fibrin from Case 1 was kept 11 days before using and that of Case 4, 12 days. Just wherein the difference of reaction lies, we are not prepared to say. Whether it is a substance mechanically adhering to the fibrin, or forming a combination with it, or a change in the composition or structure of the fibrin itself, is another problem. In connection with some other experiments in progress, the possibility of this binding action being due to associated fatty substances suggested itself.

The serum of Case 5 partially bound the complement in the presence of one non-pneumonia fibrin and completely in the presence of one pneumonia fibrin. The pericardial fluid taken from the same case at autopsy was positive in the presence of a non-pneumonia fibrin and the fibrin of Case 4.

The serum of pneumonia patients did not indicate a greater ability as shown in the experiments, before or after crisis or lysis, to bind complement in the presence of fibrin. In fact, the serum showing the greatest ability to bind complement in the presence of different fibrins was from a fatal case (No. 5), about the eleventh and fifteenth days of the disease before the temperature had fallen. The antigenic property of fibrin appears to bear no relation to the state of the disease when collected, nor does it vary with the subsequent course of the disease. Thus too, it was found that the serum of Case 5 reacted with both the fibrin of a control patient and that from a case of pneumonia.

Two attempts were made to immunize rabbits against fibrin. In the first, two rabbits were injected intraperitoneally with successive injections of powdered fibrin held in suspension in saline. After three injections, given at interval of four days, of 0.118 gms. fibrin each (approximately equal to that from 10 c.c. of blood), both of the rabbits died. A toxic peritonitis was the main finding at autopsy. All cultures were negative.

Another attempt was made with two rabbits, using smaller amounts of fibrin. The dry powdered fibrin was sterilized at 56° C. It was injected intraperitoneally in amounts varying from 0.0125 gm. to 0.025 gm., every second or third day for nine doses. Serum taken at various times did not show any antibodies toward fibrin. Neither were any fibrinolytic substances demonstrated in the serum. The serum did not possess any fibrinolytic substances when tested against pure fibrin or suspension of fibrin in agar (in petri plates).

We have found little assistance in the literature bearing directly upon our problem, though in some work done by Müller (quoted by Kossel)[1] some interesting points were brought out, indicating peptone in pneumonic sputum after crisis, but never before. He also observed the presence of a ferment in all pus-containing sputum capable of digesting fibrin, and that serous sputa and pneumonic sputa, before crisis, did not possess this power.

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[1] *Ztschr. f. klin. Med.*, 1888, 13, p. 149.

The question of the formation of auto-antibodies is rather unsettled, though not a few believe that they may occur and have been satisfactorily demonstrated. The great ability of the serum from Case 5 to react with fibrin and bind complement, as shown in our experiments, suggests that some of the toxic effects of the disease might be due to products of fibrin digestion with the appearance of antibodies in the circulation. Such decomposition products of fibrin have been shown to be toxic for animals.

GENERAL DISCUSSION.

Fibrin, in some instances, appears to be able to bind complement in the presence of serum, but the results are so irregular that they cannot be considered to be specific. Nevertheless, it is the indication of a process, the object of which is the digestion or lysis of the fibrin. Looking at it from the standpoint of auto-antibody formation, it is possible to view it as a reaction on the part of the body to rid itself of one of the products of its own manufacture. As such, fibrin does not exist in the body normally and may perhaps, on this account, act as foreign material. When the antibodies arrive in sufficient strength, the fibrinolysis begins, by the aid of complement furnished by the blood serum or leukocytes. Though the body might exhibit marked power to destroy or decompose the fibrinous exudate, in some instances, it may not possess the same ability to deal with the decomposition products.

The fact that a certain number of the "normal" sera reacted with certain specimens of fibrin is of interest, indicating the presence of substances in the serum similar to that found in a few pneumonia sera. It is possible that these reactions are not specific, but are the evidence of a previous inflammatory process of a fibrinous character.

The fact that the remains in non-resolution are principally fibrinous rather than cellular[1] indicates an absence in the body of the means of removing this portion of the exudate. If the disappearance of the fibrin be entirely due to the enzyme action of the leukocytes and of the exudated serum, it seems strange that autolysis or digestion of the exudate, except the fibrin, should go on to completion or near completion, in some cases of non-resolution, leaving the fibrin intact. It rather indicates the participation of something else in addition to the autolysis or digestion by leukocytic enzymes. Whether this persistence of the fibrin is due to a lack of preparation or "sensitization" to lysis similar to the opsonic reaction, or to an inherent antienzymotic action, or a lack of something in the body fluids designed especially to remove the fibrin, is not apparent. Though it would appear that a common process brings about the removal of the entire exudate, nevertheless, a persistence of the fibrin in spite of the disappearance of much or all of the associated exudate in some instances, points toward a process differing from that of a leukocytic digestion, though perhaps working in association with it.

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[1] Flexner, *Univ. of Penn. Med. Bull.*, 1903, 16, p. 1.

The inability to immunize rabbits against fibrin is interesting as indicating that the tissues of this animal do not react to whole fibrin. A greater number of attempts with various technics would be necessary, however, to demonstrate this more fully. It was shown by the methods used that there was no ability conferred upon the serum to decompose the fibrin.

CONCLUSIONS.

1. Human serum sometimes possesses antibodies for fibrin.
2. Fibrin is a variable factor as antigen, some specimens being able to react with many sera and some with few or none.
3. Fibrin kept in alcohol and ether loses its power as antigen.
4. The "soaping" of fibrin does not increase its efficiency as antigen.
5. Products of fibrin digestion by leukocytes do not serve as antigen.
6. Serum before and after crisis or lysis does not differ strikingly in the ability to bind complement in the presence of fibrin.
7. No relation of the ability of fibrin to act as antigen to the stage of the disease in pneumonia was apparent.

I wish to express my indebtedness to Dr. Oskar Klotz for his valuable advice and supervision of the work, and my appreciation to Dr. McMeans of the Mercy Hospital and to the St. Francis Hospital, for aid in obtaining materials.

THE ANTIGENIC PROPERTIES OF THE CONSTITUENTS OF THE PNEUMONIC EXUDATE

SERUM STUDIES IN PNEUMONIA. II

C. C. HARTMAN

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CHICAGO

THE ANTIGENIC PROPERTIES OF THE CONSTITUENTS OF THE PNEUMONIC EXUDATE.*

SERUM STUDIES IN PNEUMONIA. II.

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In a previous communication,[1] some observations were reported concerning the antigenic properties of normal fibrin and fibrin from patients having pneumonia to normal serum and serum from pneumonia patients. In brief, the main conclusion drawn at this time was that human serum (both normal and pneumonic) sometimes contains antibodies for human fibrin, which, in part, may be responsible for the dissolution of the fibrinous exudate in pneumonia.

The present report is a continuation of the studies suggested by the earlier experiments. Altho there are some points here discussed which lead us from the main trend of the work and which do not have a direct bearing upon conditions in pneumonia, they will be included, since they are interwoven with the methods used in the experiments and may aid in explaining some of the reactions observed. The same methods of securing fibrin and of carrying out the hemolytic tests were used here as in the previous work.

Since only a few specimens of fibrin showed antigenic properties to human serum, several methods to enhance this antigenic power were tried. One was to add varying amounts of a fat or lipoid solution to the fibrin. The fats used were recovered from pneumonic lungs by Dr. Oskar Klotz. The strength of the solution was the same as that used in the Noguchi test (0.3 gm. in 10 c.c. alcohol and ether [9–1], and this diluted 1 in 10 with salt solution). This dilute solution was itself found to be hemolytic in amounts of five drops. It was only slightly anticomplementary and in the presence of some sera proved to be antigenic. This antigenic property of the fats was not constant for pneumonic, normal, or positive syphilitic serum.

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*Received for publication August 15, 1913.

[1] *Jour. Infect. Dis.*, 1913, 13, p. 69.

No difference in the antigenic power of fibrin with and without the addition of the fats was found in the presence of 25 different sera, 17 being from pneumonia and 8 from normal individuals. The anticomplementary power was greatly increased by the presence of both fibrin and fats, as will be shown later.

Thirty-six specimens of fibrin (18 pneumonic and 18 controls) were used in testing the hemolytic property of the powdered fibrin suspended in salt solution. Among the 18 specimens of fibrin from pneumonia patients, 4 were found to be hemolytic. None of the controls showed this power. This power on the part of powdered fibrin to produce hemolysis was very decided when present.

The fatty substances isolated from pneumonic lungs by Dr. Oskar Klotz have been found to be very hemolytic, five drops of the 1–10 dilution in salt solution causing complete hemolysis of 1 c.c. of a 1 per cent suspension of human red cells in three hours. The fibrin suspension used as antigen was found to inhibit this hemolysis by fats when used in fairly large quantities (8–10 drops). There was evidence of a slight variation in the power of the fibrin to inhibit the hemolysis, but this was thought to be within the limits of variance of the strength of the suspension. Several specimens of fibrin from cases of pneumonia which in themselves were hemolytic did not inhibit this hemolysis and even after the extraction of the hemolytic principles by alcohol they did not inhibit the hemolysis in 25 drops (two and one-half times the amount of normal fibrin necessary completely to inhibit hemolysis). Proof of the extraction of the hemolytic principles from the fibrin lay in the finding of a hemolytic power in the alcoholic extract while the residue remained inactive.

In a series of experiments it was noted that human sera, whether normal or pneumonic, in small quantities inhibited the hemolysis by these fats. Consequently some further observations were made whereby it was shown that simple dilution with salt solution did not inhibit the hemolysis by the fats, while serum in sufficient quantities to prevent hemolysis did so regardless of the dilution (1–50). To determine whether heat had any appreciable effect upon this antihemolytic quality of the serum, several portions of a serum were treated at various temperatures—37° C. for 20 hours; 56° C. for 20 hours; 65° C. for 30 minutes; 75° C. for 30 minutes; 90° C. for 30 minutes—and afterward tested. No diminution in the antihemolytic power of the serum was found.

The protein fraction of the serum possessing this inhibitive power was then determined. The method employed by Quinan[1] was used for the fractionation of the serum. Ten cubic centimeters of normal serum (inactivated at 56° C. for 30 minutes) were diluted with 100 c.c. of distilled water. Carbon dioxid was passed through the diluted serum to saturation, causing a white, flocculent precipitate (globulins insoluble in water). This precipitate was washed thoroughly with distilled water and dissolved in 10 c.c. of saline (Solution 1). The washings and filtrate were combined and reduced by evaporation to approximately the original volume. Magnesium sulfate was added to saturation and the whole allowed to stand over night. A white precipitate appeared which was filtered off (globulin soluble in water). This precipitate was washed with a saturated solution of magnesium sulfate and redissolved in a small amount of water. Barium hydroxid was added in excess, causing a heavy white precipitate (barium sulfate and magnesium hydroxid). The precipitate was removed by filtration. The filtrate was saturated with carbon dioxid and absolute alcohol gradually added. A white flocculent precipitate separated out (water-soluble globulin). The precipitate was washed with absolute alcohol, dried with ether, then redissolved in saline (Solution 2).

The filtrate from the magnesium sulfate precipitation was dialyzed in running water for 18 hours. The remaining solution contained the albumins (Solution 3).

Each fraction was added in increasing quantities to constant hemolytic quantities of fat solution and red blood cells. The antihemolytic power of the water-insoluble globulin (Solution 1) was found to be practically equal to that of the whole serum. There was very little or no inhibitive power present in the other two fractions, the water-soluble globulin and albumin.

To determine whether the hemolytic principles were confined to any one fraction of the fats, they were fractionated according to the method used by Noguchi and Bronfenbrenner.[1] The results here given of the four fractions include also the tests of their anticomplementary power.

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[1] *Univ. of Calif. Pub.* (Pathology), 1903, 1, p. 1.

Fraction	Hemolytic	Anticomplementary
1. Ether insoluble—hot alcohol insoluble.......	–	–
2. " " — " " soluble.......	++	–
3. Ether soluble—acetone insoluble...........	+	–
4. " " — " soluble.............	+	–

Since leukocytes form such a large portion of the pneumonia exudate it was thought that they, or their decomposition products, might lead to the production of antibodies in the blood. The leukocytes were obtained from the centrifuged specimens of defibrinated blood from two cases of pneumonia, and from several abscesses and empyemas opened at operation. The organisms present in the pus were the pneumococcus, staphylococcus, or streptococcus. The leukocytes, as well as the pus, were washed thoroughly with salt solution. The leukocytes from the cases of pneumonia were immediately extracted by distilled water at 37° C. The specimens of pus were divided into portions, one being placed in 50 per cent pure glycerol, the other repeatedly extracted with alcohol and dried with ether. When used, the leukocytes were extracted by distilled water over night at 37° C., those from glycerol being thoroughly washed with saline. Chloroform, xylol, or toluol was added to the distilled water and leukocytes to prevent bacterial decomposition. The sediment was thrown down by the centrifuge.

The watery leukocytic extracts obtained in this way varied considerably; some were clear, others quite opalescent, some were hemolytic, others were not. They were not anticomplementary in small amounts and did not serve as complement. When used as antigen no constant results were obtained in regard to pneumonia sera, as is shown by the following results: The leukocytic extracts in the presence of the serum from 5 cases of pneumonia showed binding of complement; in the presence of 14 others there was no binding. In the presence of 9 of the control sera (3 with positive reactions to the Noguchi test) there was binding of complement, and in the presence of 18 other controls (5 with positive reactions to the Noguchi test) there was no binding.

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[1] *Jour. Exper. Med.*, 1911, 13, p. 43.

An interesting observation was made in the course of these experiments, in that binding occurred in the presence of all of six sera used in the tests with the extract of the cells from the two cases of pneumonia. Four of the sera were from pneumonia patients and two from controls.

One specimen of leukocytes (from pus) kept in 50 per cent glycerol when washed and resuspended in saline was not anticomplementary in small amounts, nor did it prove antigenic in the presence of one pneumonia and one normal serum. The leukocytic extracts when added to fibrin as antigen did not increase the antigenic power of the fibrin.

The leukocytic residue after extraction by water was washed in saline and used as antigen. This residue did not prove anticomplementary in small amounts. When it was used as antigen, the results were varying. The residue in the presence of one pneumonia serum bound complement; in the presence of eight other pneumonia sera there was no binding of complement; in the presence of six control sera there was binding, and in the presence of eleven other control sera there was no binding of complement. Of the control sera showing binding, one showed a positive and four a negative reaction to the Noguchi test; among those showing no binding, six showed a positive and four a negative reaction to the Noguchi test.

It was found that the residue of the cells which had been kept in 50 per cent glycerol previous to extraction was hemolytic, while that from previously dried leukocytes was not. By subjecting the hemolytic cell masses to the action of alcohol, it was found that the hemolytic principles disappeared and were demonstrated in the alcoholic extract. The residue, after the alcoholic extraction, was anticomplementary when used in large amounts, a fact which is also true for other leukocytic débris.

The nature of the fats from leukocytes was determined in a manner similar to that for the fats from pneumonic lungs. Several hundred cubic centimeters of thick, creamy pus from an abscess were incubated under toluol for several days at 37° C. Considerable change due to digestion occurred, making the pus very much more fluid. The whole was filtered and the remaining thick, greasy residue was extracted repeatedly with alcohol, then ether. The alcoholic and ethereal extracts were mixed and filtered until a clear solution was obtained. This was evaporated to dryness, leaving a thick, dark brown, fatty residue, which was divided into several portions for study.

One portion was used to test its hemolytic, anticomplementary, and antigenic power. It was found to be very hemolytic and not anticomplementary and served inconstantly as antigen in the presence of some sera.

In a series of experiments corresponding with those carried out with the other fats it was found that normal fibrin in fairly large quantities (5–10 drops) inhibited the hemolysis by the leukocytic fats. Serum was also found to inhibit this hemolysis.

An interesting observation was made when using the fat solution, the fat solution and fibrin, and the fat solution and serum with the hemolytic system. There was no anticomplementary action by the fat solution alone, the fibrin alone, or the serum alone, while increasing amounts of fat solution in the presence of a constant amount (2 drops) of normal fibrin suspension and the hemolytic system showed three reactions in regard to the hemolysis: (1) in which the fibrin and fats were in too small a quantity to inhibit the hemolysis by the hemolytic system; (2) in which the amounts of fibrin and fat solution were sufficient to inhibit completely the hemolysis by the hemolytic system; and (3) in which the fats were in sufficient excess to cause hemolysis by their own action, tho enough fibrin and fat solution were present to inhibit the hemolysis by the hemolytic system. These same reactions occurred in the presence of both normal and pneumonic serum.

Another portion of the leukocyte fats was fractionated in the same manner as the fats from pneumonic lungs and somewhat similar results found in regard to their hemolytic and anti-complementary power.

Fraction	Hemolytic	Anticomplementary
1. Ether insoluble—hot alcohol insoluble.......	−	−
2. " " — " " soluble........	+	−
3. Ether soluble—acetone insoluble...........	+	+
4. " " — " soluble.............	++	−

These four fractions were tried with a large number of sera in testing their antigenic properties. It was found that an occasional serum was positive with several portions and without regard to the result of the Noguchi test, so that any fraction may prove antigenic in the presence of some sera.

DISCUSSION.

Since the suggestion appeared in the first paper associating the antigenic property of the fibrin with fatty substances, it has been shown in our experiments that by artificial means this antigenic property of the fibrin cannot be increased by subjecting the fibrin to solutions of fatty substances. The addition of certain quantities of lipoid substances to the fibrin suspensions increased the anticomplementary property of each, a point which will be discussed again.

That a few specimens of fibrin from pneumonia patients should prove to be hemolytic is rather curious. This power is evidently due to associated fatty substances, since this property can be removed by extracting the fibrin with alcohol and it is then present in the alcoholic extract. It is perhaps true that all the specimens of fibrin used were accompanied by a greater or less quantity of fats derived, perhaps from the leukocytes, during the process of clotting. The quantity of fat present was much greater in some than the average. Why this quantity of fatty substance bound to the fibrin should be greatly increased in some cases of pneumonia is not clear, tho, if it is derived from the leukocytes, it may be the result of the increased quantity of fatty substances known to occur in the leukocytes during pneumonia and may be merely an adhesion of the fats to the fibrin.

Fatty substances extracted from the body tissues are known to be hemolytic and Lamar[1] has shown the inhibitory effect of serum upon this hemolytic action. That this inhibitive power should be limited to the one fraction of globulins is interesting and is another indication of the activity and importance of the globulin content of blood serum. Heating the serum does not interfere with this power to inhibit the hemolysis by the fats.

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[1] *Jour. Exper. Med.*, 1911, 13, p. 1.

Fibrin which in itself does not cause hemolysis will inhibit the hemolysis by fatty substances. It is interesting that a specimen of fibrin from a patient with pneumonia, which had proved to be hemolytic, when extracted by alcohol lost its power to inhibit the hemolysis by the fats. The removal of the associated fats by the alcohol would not effect this change so that a change in the fibrin itself must have been produced unless the alcohol removed substances other than the fats.

The fats isolated by the digestion of a quantity of pus were mainly of leukocytic origin, as the bulk of the pus was mainly made up of leukocytes, there being little serum present. These fats closely resembled those isolated from the pneumonic lungs. They were hemolytic and, in the presence of some sera, antigenic. This antigenic power bore no relation to the reaction to the Noguchi test. When fractionated into four fractions similar to those of the fats isolated from the pneumonic lungs, they proved to have similar properties. When these fractions were used as antigen it was found that any fraction might prove antigenic in the presence of some sera regardless of the reaction of these sera to the Noguchi test. This finding adds to the large number of substances capable of binding complement in the presence of serum.

Hiss and Zinser[1] have pointed out the beneficial effect of leukocytic extracts in the treatment of a number of infections including pneumonia. To what action this beneficial effect is due is not known. More pronounced results were obtained by their administration than by that of leukocytes or immune serum. The occurrence of a reaction to the treatment by extracts suggests the development of an immunity to them. Manwaring[2] showed the presence of bactericidal substances in leukocytic extracts which apparently are different from those in the serum, a point maintained by Schattenfroh[3] and Daeubler.[4] Buchner and Hahn[5] believe the bactericidal substances to be identical with alexine. Petterson[6] showed that the leukocytes and bone marrow are much more bactericidal in an immunized animal than in normal ones and claims that the bactericidal substances are not secreted by the leukocytes but retained in them until injured. From our results it does not appear that leukocytes act as antigen, as we were unable to demonstrate a complementary antibody with any greater frequency in pneumonic sera than in controls.

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[1] *Jour. Med. Research,* 1908, 19, p. 321.

[2] *Jour. Exper. Med.,* 1912, 16, p. 249.

[3] Quoted by Petterson.

[4] *Ibid.*

[5] *Ibid.*

[6] *Centralbl. f. Bakteriol.,* I, *Orig.,* 1905, 42, p. 56.

It is interesting that the extract of the leukocytes from the two cases of pneumonia bound complement in the presence of all the sera (4 pneumonic and 2 control) with which it was used. It may indicate that some constituents other than fats in the leukocytes in pneumonia have a greater affinity than normal for complement or that these elements are increased in this disease. The great outpouring of leukocytes into the lungs would offer a means of attracting more complement into the alveoli where it would aid in the destruction of the infecting organisms and in the removal of the exudate.

The leukocytic extracts varied, no doubt, greatly in their content, but, as Hiss and Zinser have experienced, there is no method of standardizing them nor of controlling their constancy. They have never served as complement and may prove quite hemolytic. They are anticomplementary in large amounts, but the difference between the amount used in the hemolytic tests and that used to cause binding of complement is so great that the binding in the presence of the serum cannot be due to this anticomplementary action alone. In this extraction the fats are left behind so that the constituents of the extracts are, no doubt, principally proteins.

The question of the reactions reported in these papers being due to the summation or accentuation of the anticomplementary power of the reagents has been carefully considered. It is true that the fibrin, leukocytic extracts and residues, and the fatty substances used as antigen in the experiments are in large quantities capable of preventing the co-operative action of complement with amboceptor. In the quantities used there was not sufficient present to cause any appreciable effect upon the hemolysis by complement-amboceptor action. The sera used showed no evidence of anticomplementary power in quantities at least twice as large as those used in the tests. It is true according to Noguchi[1] that the addition of one substance to another, both of which are very slightly anticomplementary, causes an increase in the anticomplementary action of the combination of the two. This increased anticomplementary power is very well shown where the addition of the fat solution to fibrin and to serum in proper proportion causes complete inhibition of the hemolysis by complement amboceptor action, neither of the substances proving anticomplementary in amounts much greater than those used in the experiment. If this same phenomenon occurs between the serum and the antigen used in other fixation tests, an endeavor must be made to measure the anticomplementary power of the combination of the two in order to correctly read the true binding of complement by the specific reaction between serum and antigen. In spite of this evidence of marked anticomplementary power of some combinations of antigens and sera, we feel that the reactions under discussion as binding of complement are true instances of that reaction.

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[1] *Loc. cit.*

A most obvious omission in these reports is the lack of consideration of the causative factor—the pneumococcus. As a word of explanation we would say that, since there is much hesitancy in accepting the pneumococcus as the center around which all the phenomena of crisis and resolution occur, it appeared desirable for us to study some of the phenomena associated with equally prominent constituents of the lung exudate. We have used each of the important constituents of the pneumonic exudate as antigen, alone and in combination with other substances, in an effort to discover a relationship to processes of immunity developed against them. Most of the results have proved negative. The frequency of non-specific binding of complement by the interaction of various antigens and sera is striking and emphasizes the necessity for very careful interpretation of all such reactions and the necessity for thorough control of all factors.

CONCLUSIONS.

1. The addition of fatty substances and leukocytic extracts to fibrin does not increase its antigenic power.

2. Leukocytic extracts, leukocyte residues, fatty substances from pneumonic exudates and from leukocytes (pus cells) cause

non-specific binding of complement in the presence of some sera regardless of the reaction to the Noguchi test.

3. Some specimens of pneumonic fibrin are themselves hemolytic.

4. Fatty substances from pneumonic lungs and from leukocytes are hemolytic, but not anticomplementary in small quantities.

5. Normal fibrin and the non-hemolytic pneumonic fibrin, human serum, normal as well as pneumonic, inhibit the hemolysis induced by these fatty substances.

6. The inhibitive power of the serum is contained in the globulin fraction precipitated by carbon dioxid.

7. The four fractions of the fatty substances from pneumonic lungs and from leukocytes simulate those used as syphilitic antigen studied by Noguchi and Bronfenbrenner in their hemolytic, anticomplementary, and antigenic powers.

8. The leukocytic extracts vary to a considerable degree in their hemolytic, anticomplementary, and antigenic properties. They do not serve as complement.

9. The residues of leukocytes kept in glycerol are hemolytic and the hemolytic principles may be extracted by and demonstrated in alcohol.

10. Extracts of leukocytes from patients with pneumonia are more strongly antigenic than those from pus cells.

11. The hemolytic substances associated with some pneumonia fibrin can be removed by alcohol, the alcoholic extract proving hemolytic.

12. The anticomplementary power of normal fibrin is greatly increased by the addition of the fatty substances used in the experiments.

My thanks are due to Dr. Oskar Klotz for his constant assistance, and to Dr. McMeans for furnishing materials.

THE BACTERIOLOGY OF SOOT

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THE BACTERIOLOGY OF SOOT*

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The study of soot from a bacteriological standpoint has received but scant attention from the numerous investigators of the problems of the smoke nuisance.

Needless to say the subject has not been left out of the discussions; in fact, it is rather frequently mentioned in a more or less general way. As far as I have been able to ascertain, however, there has been but little definite work on the Bacteriology of Soot as discussed in this paper.

In an article in the *Revue Industrielle* (1), is found the question, "Are we going to learn one of these days that smoke, thanks to its antiseptic properties, contributes to making the atmosphere healthy?" Glinzer (2) refers to the fact that the particles contained in soot possess excellent germicidal and disinfecting qualities. Racine (3) in a discussion on the "Relation of Emphysema and Tuberculosis to coal-lungs in miners," believes from his own observations that anthracosis of the lungs acts as a protective influence against tuberculosis and that the only correct view is that coal has a great disinfecting power and that the conserving action of the coal dust is perhaps to be explained "from its action as a hinderance to the growth of micro-organisms such as the bacilli of tuberculosis." We were unable to find in the literature any original work upon which these conclusions could be founded. Percy Frankland (4) shows that fogs do not tend to concentrate or nurture bacteria, for he found there were remarkably few bacteria in London air during a fog. On the other side of the question, Russel (5) includes the increased number of bacteria in a list of contributory causes of the high death rates during fogs. Sir William Ramsay (6) first brought forward the theory that smoke by directly absorbing light, through the action of clouds and fogs, which are particularly fitted to absorb the blue, the violet and ultra-violet rays, which are the germicidal rays in light, contributes to the development and increase of bacteria, pathogenic as well as others, in the atmosphere. Liefmann (7) also believes that under the above conditions "bacteria, especially the pathogenic ones, are permitted to thrive." In passing it may be mentioned that there is no evidence that bacteria ever grow in the air. They are carried into it from a variety of sources, are continually falling out of it by gravitation, being carried out by rains, or destroyed in a number of ways. The effect of the gases in the air upon bacteria is another problem, although it is closely related to the one under discussion. The contamination of the air of our cities with sulphur dioxide is well known (8); also that sulphur dioxide in the air acts as a disinfectant, the necessary proportion being not less than 92 grams of sulphur per cubic meter (9). Cohen and Ruston in "Smoke—A study of town air," have devoted some space to the consideration of the effects of acid rains upon the bacteria of the soil. They point out that the greatest reduction takes place in the numbers and the activity of the nitrifying or nitrate producing bacteria, there being also a marked inhibitory effect on the nitrogen fixing organisms.

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*This research was carried on in conjunction with the "Smoke Investigation" of the Department of Industrial Research, University of Pittsburgh.

In our investigations we examined the air of Pittsburgh to determine the numbers and distribution of bacteria in different parts of the city and to ascertain, if possible, if any relation exist between the bacterial count and the smoke conditions.

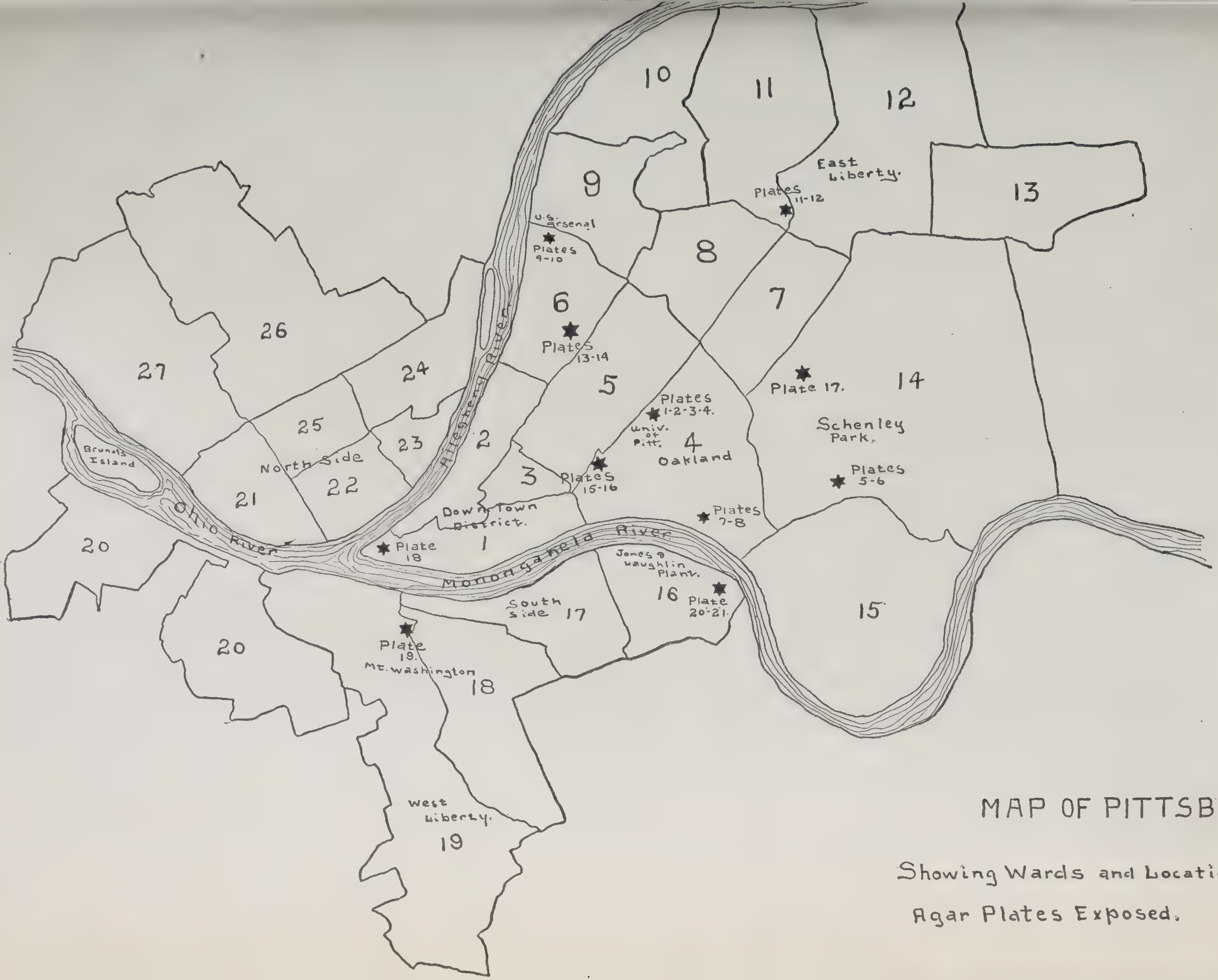
For this purpose twenty glass evaporating dishes seven inches in diameter filled with agar-agar were exposed for from five to fifteen minutes in various districts. Notes were taken of the presence or absence of smoke, the wind direction, the condition of the earth whether moist or dry, and time of exposure. The number of colonies developing in forty-eight hours at 37° C. varied within very wide limits and it was found impossible to discover any influence of the smoke content of the air on the bacterial count. The difficulty of attempting to draw any definite conclusions from these experiments will be patent to everyone, the factors which influence the bacterial content of the air being so numerous and so variable as —rain, moist or dry soil, winds, sunlight, and other conditions. The map of the city shows the points where plates were exposed and Table I gives our findings in a condensed form.

One quite striking observation, however, was made and that was the comparative infrequency of the development of colonies around the soot particles. Rough macroscopic counts were made of the total number of visible soot particles and of those which were infected, as indicated by a black speck in the center of the colony. Out of about 500 counted, 100 showed growth. Many of these particles which we counted as soot, were, in all probability, specks of dust from other sources, so that our proportion of infected soot particles is too high. In several of the plates the soot particles were too numerous to count and around the majority of these no growth was to be noted. This was particularly true in the case of Plates 9 and 10, where the atmosphere was decidedly smoky. Considering the sources from which bacteria enter the air this is not to be wondered at. The smoke as it leaves the chimney is free from bacteria and apparently is not a favorable nidus for their collection from the air into which it is poured.

The common types of aerobic Gram positive spore-bearing bacteria and

TABLE I.

Plate Number See Map.	Time of Exposure in Minutes.	Weather.	Wind.	Smoke.	Count.	Notes.
1	15	Cloudy, rain 3 hrs. before.	N. W.	None	75	B. Coli Communis isolated.
2	15	Cloudy, rain 3 hrs. before.	N. W.	"	53	
3	5	Cool, cloudy; soil damp.	W.	"	15	
4	10	Cool, cloudy; soil damp.	W.	"	68	
5	15	Clear, warm; soil damp.	W.	Blowing towards plates but high.	26	B. Coli Communis. B. Coli Communior.
6	10	Bright sunshine; soil damp.	W.		43	B. Alkaligenes. Fecalis.
7	10	Cloudy, sultry; soil dry.	S.	Blowing towards plates.	51	5 soot particles, no growth.
8	15	Cloudy, sultry; soil dry.	S.		144	15 soot particles, 3 infected.
9	10	Partly cloudy.	S.	Smoky.	60	Soot particles very numerous, 1 infected.
10	15	Warm, dry.	S.	"	108	Soot particles very numerous, 3 infected.
11	5	Clear, warm, sultry; soil dry.	S.	Hanging low.	18	Several soot particles, no growth.
12	15	Clear, warm, sultry; soil dry.	S.	Same.	46	Few soot particles; 1 infected. B. Proteus Vulgaris.
13	10	Bright, hot, dry, sultry.	S.	Valley smoke not dense near plates.	59	No soot particles. Nocardia.
14	15	Threatening rain.	S.		—	Fly contaminated plate.
15	5	Threatening rain; rain 1 hr. before.	E.	Blowing towards plates.	116	B. Pyocyaneus. Soot particles 130; 14 infected.
16	8	Threatening rain; rain began.	E.	Same.	124	Soot particles 174; 17 infected.
17	10	Threatening rain; 2 hrs. before.	E.	Air smoky.	19	No soot particles.
18	10	Hot, clear, dry, dusty.	S. W.	Dirty, dusty, smoky.	196	Soot particles 11; 4 infected.
19	10	Hot, clear, dry, dusty.	S. W.	Valley smoky, clear near plates.	160	Soot particles 19; 11 infected; air nocardia.
20	5	Hot, clear, dry, dusty.	S. W.	Blowing towards plates.	131	Soot particles 72; 30 infected.
21	10	Hot, clear, dry, dusty.	S. W.	Blowing towards plates.	128	Soot particles 56; 14 infected.



MAP OF PITTSBURGH.

Showing Wards and Location of Agar Plates Exposed.

chromogenic organisms were isolated on our plates. B. Coli Communis and Communior, B. Alkaligenes Fecalis, B. Proteus Vulgaris, B. Pyocyaneus, and others, presumably from manure dust, and a few examples of air nocardia were also found.

Our next problem was to determine the action of soot on the growth of bacteria. For this purpose a quantity of soot was obtained from the special chimney in the Department of Industrial Research.

The partial analysis was as follows:

Tar	3.84%
Ash	1.19%
Fixed Carbon	94.97%

This specimen was used throughout the experiments.

The analyses of specimens of soot collected from the air in different parts of the city showed some wide variations.

Woods Run.	
Tar	0.82%
Ash	62.6 %
Fixed Carbon	36.58%
State Hall.	
Tar	0.36%
Ash	66.68%
Fixed Carbon	32.96%

This soot, even after standing around the laboratory in an ordinary cardboard box frequently open to the air, was shown by experiment to be almost free from bacteria. Five agar plates dusted with small quantities of this unsterilized soot failed to show growth with the exception of one colony on one plate. The soot was now added in varying amounts to test tubes of ordinary broth. No growth occurred. However, when larger quantities of this same soot were added to 150 cc. of broth in flasks, growth of bacteria did appear. The organisms developing being of the B. Subtilis group.

Experiments were next undertaken to determine the bactericidal action, suggested by the above observations. Efforts were made to determine any difference in growth in flasks of broth containing soot from other control flasks without soot. Dilution and plating methods were employed but the mechanical interference of the soot particles in the one case ruled out the method as one without even approximate exactness. The counts, however, were uniformly lower in the soot broth than in the control. A series of agar plates, one having the surface sifted with soot, the other free, were next exposed in the laboratory and counts made of the colonies from the aërial contamination. No marked difference in the number of colonies was found.

The following series of experiments have, however, given us quite definite results indicating a very marked bactericidal action of soot. Five grams of soot were thoroughly mixed with 100 cc. of broth 0.6 acid to phenolphthalein. After autoclaving, the mixture was allowed to stand several days. The soot particles were then filtered out and the filtrate after sterilization was seeded with B. Typhosus. A control flask was inoculated at the same time. No growth occurred in the soot-treated broth while a good growth developed in the control.

TABLE II.

Culture.	Soot Broth.	Control.
Staph. Albus	−	+ + +
Staph. Pyog. Aureus	−	+ + +
B. Coli Communis	+ +	+ + +
B. Coli Communior	+ +	+ + +
B. Mucosus Capsulatus	+	+ + +
B. Acidi Lactici	−	+ + +
B. Typhosus (3)	−	+ + +
B. Typhosus (90)	+	+ + +
B. Paratyphosus B.	−	+ + +
B. Paratyphosus Achard	+ +	+ + +
B. Dysenteriæ (Flexner)	−	+ + +
B. Pseudodysenteriæ	−	+ + +
B. Iliacus	−	+ + +
B. Proteus Vulgaris	+ + +	+ + +
B. Alkaligenes Fecalis	−	+ + +
V. Cholera	−	+ + +
B. Pyocyaneus	+ + +	+ + +
B. Indicus	+	+ + +
B. Subtilis	−	+ + +
B. Mesentericus	−	+ + +
B. Xerosis	−	+ + +
B. Diphtheriæ (230)	−	+ + +

(The intensity of the growth is indicated by the number of + signs.)

A second experiment was carried out. The broth after treatment with soot as before was tubed and inoculated with a series of organisms. Controls of plain broth from the same batch were used for comparison. Fresh twenty-four hour cultures were employed. The results are seen in Table II.

The soot broth tubes which showed no growth after seeding and incubation, did not show any growth on further transfers with the exception of B. Subtilis. The spores in this case had most probably withstood the action of the bactericidal substance. B. Coli Communior and B. Indicus showed much less growth in the soot-treated broth than in the control. B. Pyocyaneus was apparently unaffected while B. Paratyphosus (Achard) and B. Proteus Vulgaris showed definite agglutionation in the soot-treated broth.

We believed that this inhibitory and bactericidal action was due to the phenols contained in the soot. The soot-treated broth gave a marked reaction for phenols by Millon's reagent while the control broth gave a negative reaction. After testing the acidity, phenolphthalein being used as the indicator, it was found that the soot treated broth gave a difference of 1.7 per cent. acid over the untreated broth, the acidity of which was 0.6 per cent. To determine whether this acidity was the potent inhibitory factor we carried out the following tests.

A new lot of broth was prepared and the reaction made 0.6 per cent. acid. To 500 cc. of this broth 25 grams of soot were added. The mixture was thoroughly shaken, autoclaved and allowed to stand for two days, with repeated shaking and finally filtered. The reaction titrated against N/20 sodium hydrate expressed in terms of hydrochloric acid was found to be 2.2 per cent. acid. One half of the broth was used at this acidity, 2.2 per cent. the other half being reduced to 0.6 per cent. by the addition of sodium hydrate. Half of the untreated control broth had its acidity raised to 2.2 per cent. acid with hydrochloric acid. The four lots were then tubed, sterilized and inoculated with a number of organisms from twenty-four hour agar slants. After an incubation of seventy-two hours, the results obtained were as shown in Table III.

From this it will be seen that we must consider at least two factors in the antiseptic action of the soluble content of soot in broth. The effect of the increased acidity which is seen most markedly in the cultures of the cholera vibrio where practically no growth took place in either of the acid broths is of great importance. The cholera organism is shown to be particularly sensitive to the presence of acid and for its cultivation an alkaline or neutral medium must be employed. Schroeder (10) has shown that the Vibrio choleræ is killed after an exposure of five hours to peat dust. It is especially effective, he says, if the peat dust be of an acid reaction.

The growth of B. Anthracis and B. Subtilis is also inhibited in the broths of high acidity, while B. Alkaligenes Fecalis and B. Iliacus, are definitely affected. It is interesting to note the effect of the acidity in interfering with the production of the coloring matter in the cultures of B. Pyocyaneus. Russel, Cohen and Ruston, and others point out the variable acid content of soot. On the other hand we notice, that, independently of the acidity, the soot-treated broth exercises a marked interference with growth. This is to be seen with B. Indicus, one strain of B. Coli Communis, B. Typhosus, and in B. Paratyphosus to a marked degree. The two latter organisms are not generally affected by small amounts of acid, and are, therefore, valuable in testing out this second bactericidal effect of the soluble parts of the soot.

Soot probably has the power of absorbing many gases from the air especially those associated with the combustion of coal.

The next problem was to study the effect, if any, of soot on the destruction of bacteria in the process of dessication.

TABLE III.

Culture.	Control Broth. 2.2 Acid.	Soot Broth. 2.2 Acid.	Control Broth. 0.6 Acid.	Soot Broth. 0.6 Acid.
B. Indicus......	Heavy cloud.	Trace of cloud.	Heavy cloud, heavy precipitate.	Slight cloud.
B. Pyocyaneus ..	Heavy cloud, powdery scum, trace of green color.	Same, no green color.	Same, bright green on top.	Heavy cloud, thick compact scum, green color throughout.
B. Anthracis....	Clear, no precipitate.	Clear, no precipitate.	Clear, abundant precipitate.	Clear, slight precipitate.
B. Subtilis......	No growth.	No growth.	Heavy ring, heavy precipitate, granular cloud.	Ring on glass, precipitate.
B. Coli Communis (52) and (14)..........	Marked cloud.	Slight cloud.	Marked cloud.	Slight cloud.
B. Coli Communis from urine (780).........	Fair cloud.	Same.	Same.	Same.
B. Typhosus....	Cloud.	Slight cloud.	Heaviest cloud.	Faint cloud.
B. Paratyphosus B............	Marked cloud.	Faint cloud.	Marked cloud.	Faint cloud.
B. Proteus Vulgaris.........	Heavy cloud, no scum.	Heavy cloud, scum.	Very heavy cloud, no scum.	Very heavy cloud, scum.
B. Iliacus.......	Slight cloud.	Fair cloud.	Heaviest cloud.	Heavy cloud and ring.
B. Alkaligenes Fecalis.......	Faint cloud.	Clear.	Marked cloud, scum.	Slight cloud.
V. Cholera......	Clear.	Trace of cloud.	Cloud.	Cloud.

Dessication is one of the most valuable natural means of disinfection and many organisms succumb to its effects very rapidly as the gonococcus, the B. Influenza, the meningococcus and others. The micro-organisms of the air, on our streets, and in our houses are continually being destroyed by this process and we have been able, we believe, to show that soot increases very decidedly, this bactericidal action.

TABLE IV.

Exposure.	Influence of Soot on B. Indicus.		
	Control. Cover Glass. Dipped in Broth and Dried.	Cover Glass I. Dipped in Soot while Moist, then Dried.	Cover Glass II. Dried as in Control. Buried in Soot.
1 day	+	+	+
2 "	+	+	+
3 "	+	+	+
4 "	+	−	+
5 "	+	−	+
7 "	+	−	−
8 "	+	−	+

(The + sign indicates that growth was obtained in the test cultures.)

TABLE V.

Exposure.	Influence of Soot on B. Typhosus and Streptococcus Fecalis.			
	Culture.	Control. Dipped in Broth and Dried.	Cover Glass I. Dipped in Soot while Moist, then Dried.	Cover Glass II Dried as in Control. Buried in Soot.
2 days	B. Typhosus	+	−	
	S. Fecalis	+	+	
3 "	B. Typhosus	+	−	+
	S. Fecalis	−	−	−
	B. Typhosus	+	−	+
	S. Fecalis	+	−	+
4 "	B. Typhosus	+	−	+
	S. Fecalis	−	−	+
5 "	B. Typhosus	+	−	+
	S. Fecalis	+	−	−
6 "	B. Typhosus	+	−	+
	S. Fecalis	−	−	−
9 "	B. Typhosus	+	−	+
	S. Fecalis	−	−	−
10 "	B. Typhosus	+	−	−
	S. Fecalis	+	−	−

The technique of our experiments was as follows: Fresh twenty-four hour-broth cultures of the organisms to be tested were prepared. Small sterile cover glasses were thoroughly moistened by dipping them into the cultures. These were dried under sterile precautions for sixteen to twenty-four hours over caustic soda. They were then transferred to sterile petri dishes and used as controls.

Cover glasses indicated under the heading I in the table, were dipped into the broth cultures and then into sterile soot and finally dried as in the control. Cover glasses under heading II in the table were prepared in the same way and at the same time as the control, and when dry were packed in sterile soot. From time to time these cover glasses were dropped into tubes of dextrose broth to test the viability of the organisms.

It will be noted that the failure of growth is shown very clearly in the case where the moist cover glass was dipped in soot and then dried. In the majority of cases those cover glasses which were first dried and then packed in soot failed to show growth much later than the above, but usually before the control. This is well shown in Table V.

The long period that the Streptococcus Fecalis, 174 days, and Staphylococcus Pyogenes Aureus, 225 days, remained viable under these abnormal conditions, is quite remarkable. (See Table VI.)

In Table VII is shown the peculiar behavior of yeast. It survived longest, 41 days, on the cover glasses dipped in soot while still moist, the conditions under which all the other organisms tested rapidly died out. Marshall (11) quotes Hansen as stating that compressed beer yeast mixed and dried with charcoal kept as long as ten years. The marked resistance of the yeast organism to the action of acids is also of importance in this connection.

The great natural disinfectant of the atmosphere and our surroundings is the bactericidal action of the sun's rays. Direct sunlight is most destructive and its activity upon bacterial life depends directly on the amount of moisture and dust in the air.

Smoke, in contributing very great numbers of minute particles to the air, adds to the conditions favoring fogs and clouds. Smoke, fogs, and clouds, all absorb more or less, the blue, the violet, and ultra-violet rays of the sunlight. This is well seen in the familiar red sun of a smoky atmosphere. These particular rays, which are absorbed, give the important bactericidal action to the sunlight. Most of the above facts have been amply proved by other experiments and it was not considered advisable to repeat them. We have, however, made a few observations on the protective action of soot for bacteria.

The technique of our experiments was briefly as follows: Agar-agar, well seeded with the test organism, was poured into petri dishes. Soot was sifted over one half of the cover of the petri dish while the other half re-

TABLE VI.

Time of Exposure.	Incubation Period.	Influence of Soot on B. Coli, B. Typhi, Streptococcus Fecalis and Staphylococcus Aureus.			
		Culture.	Control. Dipped in Broth and Dried.	Cover Glass I. Dipped in Soot while Moist, then Dried.	Cover Glass II. Dried as in Control. Buried in Soot.
2 days.......	24 hours	B. Coli	+	+	
		B. Typhosus	+	+	
		Strep. Fecalis	+	+	
		Staph. Pyog. Aureus	+	+	
5 “	24 “	B. Coli	+	−	+
		B. Typhosus	+	+	+
		Strep. Fecalis	+	−	+
		Staph. Pyog. Aureus	+	−	+
	48 “	B. Coli	+	+	+
		B. Typhosus	+	+	+
		Strep. Fecalis	+	−	+
		Staph. Pyog. Aureus	+	−	+
6 “	24 “	Strep. Fecalis	+	+	+
		Staph. Pyog. Aureus	+	−	+
7 “	24 “	B. Typhosus	+	−	+
		Strep. Fecalis	+	+	+
19 “	24 “	B. Coli	+	−	+
		B. Typhosus	+	−	−
		Strep. Fecalis	+	−	+
		Staph. Pyog. Aureus	+	−	+
	48 “	B. Voli	+	−	+
		B. Typhosus	+	−	−
		Strep. Fecalis	+	+	+
		Staph. Pyog. Aureus	+	−	+
34 “	24 “	B. Coli	+	−	−
		B. Typhosus	+	−	−
		Strep. Fecalis	+	−	+
		Staph. Pyog. Aureus	+	−	+
	48 “	B. Coli	+	−	−
		B. Typhosus	+	−	+
		Strep. Fecalis	+	−	+
		Staph. Pyog. Aureus	+	−	+

TABLE VI (*Continued*).

Time of Exposure.	Incubation Period.	Influence of Soot on B. Coli, B. Typhi, Streptococcus Fecalis and Staphylococcus Aureus.			
		Culture.	Control. Dipped in Broth and Dried.	Cover Glass I. Dipped in Soot while Moist, then Dried.	Cover Glass II. Dried as in Control. Buried in Soot.
62 days......	24 hours	B. Coli	+	–	–
		B. Typhosus	–	–	–
		Strep. Fecalis	–	–	–
		Staph. Pyog. Aureus	–	–	–
	48 “	B. Coli	+	–	–
		B. Typhosus	–	–	–
		Strep. Fecalis	+	–	+
		Staph. Pyog. Aureus	+	–	+
174 “	24 “	Strep. Fecalis		–	+
		Staph. Pyog. Aureus	–	–	+
225 “	24 “	Staph. Pyog. Aureus	+	–	–
247 “	24 “	Staph. Pyog. Aureus	–	–	–

mained free. These plates were then exposed to the sunlight for definite periods, then incubated and the results read.

A number of plates, seeded with Staphylococcus Aureus, were exposed to sunlight for varying periods every day for two weeks. The results obtained are shown in Table IX. Notwithstanding the irregularity of these results the protection, afforded by the soot in the air and clouds against the action of the sun's rays, is, I believe, clearly shown.

There are a number of very interesting questions which arise as a result of these experiments. It has been shown that soot in contact with bacteria has very decided bactericidal properties. These properties are also demonstrated in the soluble content of the soot. The soot particles from the air as they fell on our plates were generally sterile. This may be due to the solution of the bactericidal substances of the soot by the moisture on our plates, with the consequent destruction of any bacteria adherent to the soot. Or the moisture condensing around the soot as it does in the formation of fogs and clouds, may have acted in the same way before it was collected on our plates. The third possibility is that the majority of the soot particles never came in contact with bacteria after leaving the chimney, at which time they were, of course, bacteria free.

That this disinfectant substance requires moisture in order to have its most powerful effect is well shown in the drying experiments where the organisms treated with soot, while still moist, succumbed very much sooner than the others. There is also the possibility that the soot absorbs moisture from the bacteria and hastens thereby its death by thorough drying. This was suggested in the experiment in which dried organisms were buried in soot and frequently killed off earlier than in the control.

TABLE VII.

Time of Exposure.	Incubation Period.	Influence of Soot on B. Diphtheriæ and Yeast (Saccharomyces).			
		Culture.	Control. Dipped in Broth, then Dried.	Cover Glass I. Dipped in Soot while Moist. Dried.	Cover Glass II. Dried as in Control. Buried in Soot.
3 days......	48 hours	B. Diphtheriæ	+	−	
		Yeast	+	+	
	72 "	B. Diphtheriæ	+	+	
		Yeast	+	+	
7 "	24 "	B. Diphtheriæ	+	−	+
		Yeast	−	−	−
	48 "	B. Diphtheriæ	+	−	+
		Yeast	+	+	+
	72 "	B. Diphtheriæ	+	+	+
		Yeast	+	+	+
16 "	48 "	B. Diphtheriæ	+	−	+
		Yeast	−	+	+
	72 "	B. Diphtheriæ	+	+	+
		Yeast	−	+	+
27 "	72 "	B. Diphtheriæ	+	−	+
		Yeast	−	+	−
38 "	48 "	B. Diphtheriæ	+	−	+
	5 days	B. Diphtheriæ	+	+	+
41 "	48 hours	B. Diphtheriæ	+	−	+
		Yeast	−	+	−
77 "	72 "	B. Diphtheriæ	−	−	−
		Yeast	−	−	−

That the conditions, similar to those of our experiments, are to be found in every smoky city, will be evident to any one who has noticed the black, smeary deposit of soot on damp days where the concentration of soluble

TABLE VIII.

Organism Tested.	Inhibition of Solar Bactericidal Activity.			
	Time of Exposure.	Incubation.	Soot Covered Half.	Unprotected Half.
Strep. Fecalis	5 mins.	24 hrs.	Few colonies	None
	5 "	48 "	Many "	Many colonies
	15 "	48 "	Few "	No growth
	30 "	48 "	Few "	Many colonies
	45 "	48 "	Few "	Many "
	45 "	48 "	Many "	Few "
	120 "	48 "	Many "	Few "
B. Indicus	10 "	48 "	Many "	Many "
Staph. Aureus	10 "	48 "	Many "	Many "
	30 "	48 "	Many "	Many "
	45 "	48 "	Many "	Few "
	75 "	48 "	No "	No "
B. Mesentericus	15	48 "	Few "	Few "
	30 "	48 "	Few "	Few "
	45 "	48 "	Few "	Few "
	60 "	48 "	Few "	Few "
	75 "	48 "	Few "	Few "
	180 "	48 "	Few "	Few "

substances from the soot in crevices and corners must be very high. We have found, as others have demonstrated that the effect of soot in fogs and clouds in diminishing the action of the sun's rays on bacteria, is quite definite. The relative importance of the protective qualities of soot against sunlight to the bactericidal effect of the constituents of soot remains an open question.

There are, therefore, two divergent results brought about by the presence of soot in our atmosphere and upon the earth's surface. One of these is beneficial and the other harmful to the life of vegetable micro-organisms, and from the bacteriological and hygienic point of view may serve as a direct aid in propagating or preventing the spread of infectious disease.

General Conclusions.

1. Soot has a definite bactericidal action on bacteria, due either to the absorption of moisture from the organisms or more probably to the action of its contained germicidal acids and phenols.

2. Soot as it exists in the air does not form a favorable nidus for the collection and distribution of bacteria.

TABLE IX.

(Inhibition of Solar Bactericidal Activity by Smoke. Test Organism Staphylococcus Pyogenes Aureus)

	Sun.	Clouds.	Smoke.	Result.	Note.
1	Bright		Clouds low.	Killed 1 hr.	
2	Dull	Present.	Clouds passing over sun.	Slight difference in 1 hr.	
3	Bright	Passing across sun.	None.	Killed 1 hr.	24 hr. incub.
4	Bright	Same.	"	Lessened in 15 and 30 mins. in proportion.	
5	Hidden, dull	Snowing in morning. Present.	"	Killed in 1½ hrs.	
6	Bright	Thin and white.	Around horizon.	Not killed in 1 hr., lessened.	
7	Clear	—	Haze around horizon.	Same.	
8	Bright and clear	Very few.	—	35 mins., much lessened; 1 hr., almost all killed.	
9	Bright and variable ..	Cloudy.	—	Not killed in 1 hr.	
10	Bright	None.	Much, low down.	Not killed in 1 hr.	Around edge.
11	Dull, foggy.	Foggy.	—	Little change in 1½ hrs.	
12	Dull	Many, raining.	Much.	Almost all killed in 1½ hrs.	
13	Variable, free, dull	Variable.	—	Little change 1¾ hrs.	
14	Bright	None.	Haze.	Killed in 1 hr.	

3. Broth and other fluids treated with soot have conferred upon them a decided germicidal power.

4. This germicidal action is due not only to the acids contained in the soot but also to some other agent, probably some of the phenols.

5. Soot, as it occurs in smoke, clouds, fogs, and as a non-transparent covering for our streets and houses, protects micro-organisms from the destructive action of the sunlight.

I wish to express my thanks to Mr. C. H. Marcy for his valuable assistance in the early part of the work, more especially in the study of the

bacteriology of the air of Pittsburgh. I wish also to thank Dr. O. Klotz for many suggestions and Mr. Benner for the samples of soot and the chemical analysis of the same.

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SPONTANEOUS AND ARTIFICIAL DEVELOPMENT OF GIANT CELLS *IN VITRO.*

By G. C. WEIL.

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SPONTANEOUS AND ARTIFICIAL DEVELOPMENT OF GIANT CELLS *IN VITRO*.[1]

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During the study of the growth of various tissues in different culture media, our attention was repeatedly attracted to the occurrence of giant cells among the newly formed tissues. Such giant or multinucleated cells appeared to develop without any regularity as to the nature of the medium in which they were growing or to the presence of known stimuli artificially introduced. However, on closer observation, it appeared that certain external influences did have their effect in leading to the occurrence of multinucleated cells. As to the nature of these influences, we were, in many instances, unable to come to a conclusion. Thus it was noted that in some sets of cultures the development of multinucleated cells from fibrous tissue cells was more common than in others, and so, too, certain cultures of heart muscle showed a greater frequency of cells with multiple nuclei than appeared in others under apparently the same technique.

The study of multinucleated cells of connective tissue and muscle can be carried on with greater ease and more security of proper interpretation of their source than is possible with the study of the multinucleated cells having origin in wandering cells—namely, in the first two types, it is always possible to pick out cells which, though isolated from the surrounding tissues, still preserve a connection with one or more cells whose nature is definitely known. Moreover, the arrangement of these cells can be accurately tabulated, so that in the continued study of the same cells it is possible to recognise the original architecture and to observe whether any new cells have entered into the formation of the developing giant cell.

From our observations on the development *in vitro* of multinucleated cells from different tissues, we have been led to consider them as having a common method of origin. There is, however, this difference, that the factors which stimulate their production are to some extent different among the various types of cells; whereas the nature of the stimuli which act upon the fixed tissue cells, causing

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them to possess many nuclei, is of a different nature from that which acts upon the wandering cells; the difference is more one of degree than of quality. It is probable that the irritant acting upon the fixed tissue cells is in solution, while the mere presence of foreign particles does not readily influence them. Thus the development of multinucleate characters is the result of a particular irritation of the cells, causing them to react in an abnormal fashion in their subsequent development of growth.

While our own observations on the development of giant cells *in vitro* were in progress, similar observations were reported by Lambert (1912 [2]). This author was particularly interested in the artificial production of foreign body giant cells in cultures from the spleen. He developed the unique method of introducing lycopodium spores into his culture along with the growing tissues, and by observing the reactions and changes which took place in cells immediately about the lycopodium spores, he came to certain conclusions. Our own observations upon wandering cells had previously been made upon cells from the same organ (spleen), which had grouped themselves around foreign bodies (cotton fibres and débris), accidentally introduced. Subsequently, however, we have made use of Lambert's method, which we have found to be very satisfactory.

A great number of cultures were made from different tissues and organs, as well as from chicks of various ages (varying from six to twenty days). In agreement with Lambert, it was found that in cultures of connective tissues, muscle, cartilage, and surface epithelium the introduced lycopodium had no effect upon their morphology. These tissues, as has previously been pointed out, not infrequently showed the presence of giant cells, but the production of these cells did not appear to be associated with the presence of foreign bodies.

The presence of foreign bodies in the cultures of spleen tissues was, on the other hand, quite effective in altering the morphological characters of some of the elements. In carefully observing the individual cells, as they appeared in the culture medium at some distance from the originally implanted mass, we were not infrequently able to follow the life-history of isolated cells or cell masses. The presence of foreign material in the culture medium had the effect of producing a fairly definite sequence of events, as was indicated in the successive migration of cells with the subsequent changes in them. This process is of particular interest on this occasion, and of it we wish to speak in greater detail.

The preparation of these cultures was quite similar to the hanging-drop preparations as described by Lambert (1912 [2]) and Carrel (1911 [1]). The sterile lycopodium granules were introduced either before or during the preparation of immediate cultures. Small portions of spleen tissue were introduced into the culture medium with or without previous washing in Ringer's solution. The primary washing had the effect of ridding the tissue of many of its red blood cells.

Within the first twenty-four hours after implantation, great numbers of red blood cells were diffused at some distance from the tissue mass, and with them a few leucocytes were to be seen making their way from the periphery. Small mononuclear cells were also present in varying numbers. This immigration of leucocytes and lymphocytes continued for several days, while with their increase the red cells gradually disappeared. Nevertheless, well preserved red blood cells were present close to the spleen tissue after sixty hours. During the early periods (thirty-six to forty-eight hours) of the culture, the leucocytes showed a great amœboid activity, wandering at some distance from their origin and taking up a position around the foreign bodies in the medium. Gradually, after several days, the lycopodium seeds which were scattered through the otherwise homogeneous medium became surrounded by dense clusters of polymorpho-nuclear leucocytes, in which a fair number of lymphocytes were to be observed. We continued to make repeated observations upon these aggregations of leucocytes, and it was observed that their phagocytic activity remained quite pronounced for six days, and even up to the eighth day of the culture. At this time, however, many of these cells were showing the effects of degeneration, some with fat in their protoplasm, others showing an actual cytolysis.

The crowding of these leucocytes and lymphocytes around foreign particles, and particularly when observed at the time of partial degeneration, gave a false impression of their structure. A hurried examination gave the impression of a large syncytial mass containing small and irregular nuclei. A closer study of such masses allowed a correction to be easily made. It is, however, well to point out that some misinterpretation in the study of these tissues is very liable to occur when well-stained preparations are not at hand. We have found that certain masses which had every appearance of multinucleated cells, resolved themselves into fused aggregations of the homogeneous débris of degenerating cells. In our hands it has been found best to study cultures of different ages, fixed in pure methyl alcohol, and stained by Wright's or Giemsa's solutions.

Not only does some difficulty present itself in differentiating the boundaries of mononuclear cells which are mechanically incorporated in the mass of degenerating cells, but as new cells attach themselves to the periphery of the mass in succeeding crops, some of the outermost cells have the appearance of undergoing fusion.

In the above observations we are dealing with cells of leucocytic and lymphocytic variety which, all are agreed, never play any part in the formation of true giant cells.

Following the first outwandering of polynuclear leucocytes there appeared a cell possessing amœboid motion, which slowly made its way towards the periphery of the culture medium. This cell could be distinguished from the growth of the spindle-shaped connective-tissue cells which radiated and for the most part remained attached to the original mass. These new cells appeared after the first twenty-four hours and continued to increase for a day or two. Individual large cells could be observed and studied in the medium quite free from other cells. During the early stages of migration, the rich protoplasm of these cells was homogeneous and took a faint blue stain. The nucleus was rather large and spherical. As these cells became older, and we were able to observe them over considerable periods of time, the protoplasm changed from having faintly basic characters to that in which the eosin stain gave a faint pink reaction. The intensity of the pink staining increased with the age of the cell and the process of degeneration. Moreover, degeneration was also indicated by the development of granules in the protoplasm, some of which were of a fatty nature.

By their amœboid activity these cells wandered towards foreign particles and attempted to engulf them. Where these particles were small the cells incorporated them within their protoplasm. We have observed a similar phagocytosis of bacteria. On the other hand, where the foreign materials were of large size, the cells tended to lie close to these masses and to flatten out their protoplasm against their sides. At times a mass of these large mononuclear cells alone would be attracted to the same particle. More frequently were they to be found mingled with the polynuclear leucocytes which had preceded them.

In following up the subsequent history of those cells which had arranged themselves around foreign material, it was possible, by making observations at short intervals, to note the gradual inclusion of the foreign body by a syncytial mass. The complete inclusion was more commonly observed at about the sixth day, when the activity of the other wandering cells was diminishing.

Upon examination of the lycopodium granules on the fifth and sixth day of growth, we found them completely surrounded on all sides by cellular material. Those leucocytes and lymphocytes, which were first attracted by the lycopodium granules, now appeared as a homogeneous mass, having little or no cellular structure, while a few cells close to the outer margin, which arrived later, still retained their original shape. About the extreme outer margin were several layers of endothelial-like cells, which were just beginning to show evidence of degeneration.

Examination of the culture field at this time, in parts containing no foreign particles, showed some of the leucocytes still very active, while the large round endothelial-like cells contained a great number of fatty granules which were doubly refractile, under Nicol's prism. Again, in some instances, we found layers of leucocytes massed together where no foreign particles existed other than a few red blood cells. The cells of the central portion of these clumps had lost their power of amœboid motion and showed cellular degeneration, while about their periphery we found them still retaining this property. Where masses of these large protoplasmic cells (presumably endothelial cells) were aggregated into a cluster surrounding a foreign particle, the further changes in their structures and arrangement could be followed only by making observations at short intervals. The main feature which may be brought out by such observations is the answer to the question,—whether new wandering cells are coming to, and fusing with, this mass to enter into giant cell formation. By closely following a series of such observations, we have found that masses composed of a known number of these large wandering cells retained the outlines of each cell, until in a process of degeneration, evidenced by the increased eosin staining qualities and the development of fat droplets within the protoplasm, the protoplasm of neighbouring cells becomes fused at their borders.

In unstained preparations it was impossible to observe the process of division of the nuclei that occurred in the growing cells. We found that when specimens were continuously exposed to the intense light necessary for microscopic examination, the cultures suffered in their growth. Therefore the observations were made at intervals of one hour.

By obtaining a good low power sketch of these cells in the surrounding field, and comparing this with the findings at the stated periods, it was possible to keep count of the number of new cells arriving in the mass. By the later comparison of the figures of the total number of cells thus observed with the number of nuclei obtained in the stained preparation, a definite knowledge of the increase of the nuclei was possible. In some cases this increase amounted to a two- or three-fold number over the entire number of cells known to have migrated to the part. In a few instances where an accurate account of the migrating cells was not made, syncytial masses containing as many as forty nuclei were, later, demonstrated in stained preparations. Fusion of the active and healthy cells was not observed in our preparations. We believe that by this method of observation an accurate count of the cells and nuclei wandering toward a given area may be obtained and compared with the number of nuclei at the end of different time limits.

Repeated examinations of favourable preparations showed the gradual enlargement of one or more of the mononuclear cells in contact with the foreign body. The boundaries of the "flowing" protoplasm of these cells were difficult to define until well stained. We were thus forced to stain many preparations when the appearance of fusion was obtained in the fresh culture, only to find that the cell boundaries remained distinct while the cell was active. New nuclei appeared from time to time, but the actual development of these we did not observe. This, however, has previously been commented upon. When, however, we found a preparation which had been closely followed, in which a giant cell with thirty nuclei had developed, we felt positive that these nuclei did not appear in the part by the process of migration of thirty cells.

In conjunction with the observations upon these wandering cells, studies were also made upon multinucleated cells in other tissues. Greatest attention was given to the multinucleate cells of connective tissue. In these instances it was fairly easy to pick out different cells for observations. These cells commonly showed strands of connection running to other connective tissue cells. By obtaining a clear picture of such connections with the neighbouring cells, it was possible to observe changes in the relative position of these cells to each other and to exclude the possibility of cells from similar tissue fusing with the cell under observation. In no instance did we observe the approach of such cells to each other to fuse into a larger syncytial mass, while the development of multinucleate cells is not infrequent in this tissue. Similar observations upon growing muscle fibres demonstrated the development of large protoplasmic cells with many nuclei by a process of endogenous nuclear multiplication.

SUMMARY.

In our observations upon cultures of spleen tissue it was observed that the presence of foreign particles caused a definite sequence in the migration of different forms of the wandering cells. The polymorpho-nuclear leucocytes were the first cells to respond and to aggregate themselves about foreign masses. These were shortly followed by lymphocytes. Following these at an interval of twenty-four to forty-eight hours, there appeared a large mononuclear and protoplasmic cell, which had the characters of an endothelial cell. By the time of the appearance of this cell, some of the polymorphonuclear cells were undergoing disintegration. These large endothelial cells had phagocytic qualities and tended to surround the foreign particles in the medium. By keeping accurate records of the numbers of cells migrating to a given point, it was possible to account for the number of nuclei (within a narrow limit of error) of the cells which migrated to the part. This count was compared with the numbers of nuclei determined in stained sections at the end of the observations.

In our preparations we have not observed the fusion of cells to form multinucleate ones, save where the cells involved were undergoing degeneration. Where this process of fusion occurred, the cells did not exhibit subsequent phagocytic activity.

We have, however, obtained multinucleate characters in cells lacking any sign of degeneration and still showing power to engulf foreign particles. These giant cells were obtained in a process of nuclear division without visible protoplasmic change.

It would thus appear from our observations that *in vitro* the multinucleated cell arising from the large mononuclear endothelial cell has the same mode of origin as the multinucleate cells of fixed tissues as are constantly observed in cultures of connective and muscle tissue cells.

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SOME HISTOLOGICAL EVIDENCES OF THE DISEASE IMPORTANCE OF PULMONARY ANTHRACOSIS

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SOME HISTOLOGICAL EVIDENCES OF THE DISEASE IMPORTANCE OF PULMONARY ANTHRACOSIS.*

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The histological evidences as to the disease importance of anthracosis of the lungs, as set forth in this paper, are the results of work done by the author in an attempt to determine whether or not extensive deposits of dust and coal pigment within the body tissues have or have not any "real disease" significance. The problem as originally planned included a study of all of the microscopic effects of smoke and soot upon the body as a whole. Such a piece of work has been impossible in the time at our disposal so that in the present paper we shall deal only with the microscopic effects of smoke and soot, as observed upon the air passages and lungs, which are the chief portals of entry for these substances into the body. We have also included a consideration of the association of the resultant pulmonary lesions with those of tuberculosis and pneumonia.

The paper naturally divides itself into three parts, and for the sake of clearness these will be discussed under the headings of: I. The anthracotic process; II. The association of anthracosis and tuberculosis; and III. The association of anthracosis and pneumonia.

In the use of the term anthracosis in this report it must be understood that it refers only to the fairly well advanced stages of the process, as will subsequently be described.

The tissues studied were obtained in part from the surgical and autopsy materials of the Department of Pathology of the University of Pittsburgh, and from the Mercy Hospital, and in part from experimentally produced lesions in animals.

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I. The anthracotic process. — Anthracosis is a term applied to a condition in which carbon particles of extraneous origin are deposited in the tissues or organs. It has been described as occurring in the lungs, spleen, liver, intestinal tract, and certain sets of lymph nodes, and is always accompanied by more or less fibrosis on the part of the tissues in which it is found. The most common site for anthracosis is in the lungs, and in individuals who work or live in smoky, sooty atmospheres it often reaches a marked degree of development.

The fine particles seem to gain entrance into the lung substance by way of the air passages, and it has been stated by some that the mucous membranes of the nose, mouth, pharynx, larynx, trachea, bronchi, and bronchioles contribute largely to the taking in of the pigment, but our observations tend to show that in this community (Pittsburgh), at least, such is not the case. In the nasal cavities, the vibrissæ, and turbinates collect a great deal of carbon, which is subsequently removed by the secretions, for in the examination of nasal polypi and strips of turbinate mucosa removed at operations we have never seen a single example of free pigment or pigment bearing cells beneath the epithelial layer. Maclachlan[1] in his paper on "Tonsillitis" in which he reported a histological study of three hundred and fifty pairs of tonsils found only one example of a carbon pigment bearing cell in that structure, and about as many more tonsils and adenoids have since been examined without finding another instance. In the air passages below the larynx, pigment bearing cells have frequently been observed, but these were either free in the lumen or were surrounded by bits of mucus and other cells and were not found penetrating the epithelial layers. In abscesses of bronchi, both the abscess contents and remaining parts of the mucosa have been seen to contain pigment bearing cells, though one could not say that any of these were definitely passing into the tissues. Moreover, our contention is supported by the following two experiments:

Experiment I. — For twenty minutes daily a young guinea-pig was placed in a box through which a dense black smoke was made to pass. The smoke was generated by burning xylol and entered the box through a funnel. After each exposure the animal showed a profuse nasal secretion and sneezed repeatedly. His furry coat was completely blackened. At the end of ten days he was killed with chloroform and autopsied. Macroscopic description: The gross findings of soot deposit were entirely limited to the blackened nasal mucosa, which was especially marked over the anterior portions of the turbinates. Microscopic description: Sections showed soot particles adherent over the epithelium of the nasal mucosa. There was no evidence of pigment phagocytosis. (*Note.* — Notwithstanding the fact that three guinea-pigs with early spontaneous anthracosis have come under our notice we failed in our attempts to reproduce the condition experimentally, apparently on account of the efficient way in which the intricately arranged turbinates protected the air passages beyond them.)

Experiment II. — A white rabbit was given sixty inhalations in eighty-seven days of finely powdered lamp black in the following way: The nose piece of a powder insufflator was placed in the animal's mouth and the lamp black was forced in under pressure. At first the inhalations were given every two or three days, but later the treatment was carried out daily. The animal became very much emaciated and died. The autopsy was performed while the tissues were still warm. Macroscopic description: All of the mucous membranes of the mouth, pharynx, esophagus, stomach, larynx, trachea, and bronchi were coated or crusted with black pigment. Many of the lesser bronchi were completely plugged with masses of lamp black so that the foci of lung beyond them were devoid of air and in a stage of collapse. A few fine black granules were seen in the lung tissue. Microscopic description: In no part of the upper air passages was the phagocytosis of pigment observed. No pigment was seen in or beneath the epithelial layers of the bronchi, though some of them contained sufficiently large masses of pigment in their lumina to cause a flattening of the epithelial lining cells. In the alveoli many pigment phagocytes were seen (Fig. 7), and these cells were especially numerous in the atelectatic areas; some of them had already penetrated into the spaces of the alveolar walls, but as yet none had reached the perivascular, peribronchial, or subpleural lymphatics. The peribronchial lymphoid tissue was also free from pigment. The carbon pigment cells were large and round and were so completely filled with granules that their identity was obscured.

It will be seen by these two experiments that although we were able to bring an abundance of carbon pigment in direct contact with the epithelial linings of the oral cavity and upper air passages we were unable to obtain any evidences of phagocytosis of such pigment in any of these structures. Coupling these results with our negative findings in the surgical and autopsy materials cited above, we feel justified in concluding that the amount of pigment phagocytosis in the air passages above the lung alveoli must be a negligible quantity.

As our studies on the anthracotic process have to do largely with the lung alveolus and with the lymphatics of the lung a hasty review of our knowledge of these structures seems advisable at this point.

The alveoli, or air sacs, are minute cuboidal or spheroidal cavities which open directly into the small bronchioles through the infundibuli. The cavities are lined by a single layer of very flat pavement cells, which rest on a very thin basement membrane. Small openings called stomata sometimes connect one alveolus with its neighbor. The walls contain both smooth muscle and elastic tissue and are exceedingly vascular. The vessels are capillaries with definite endothelial walls, and they form a network completely surrounding the alveoli.

The lymphatics have their beginning as small intercellular spaces in the alveolar walls. These connect with larger lymph spaces in the interlobular septa, which then empty into definite channels also having endothelial linings. These latter channels are found in three sets which are called, according to their location, perivascular, peribronchial, and subpleural. The larger channels have valves and foci of lymphoid tissue distributed along their courses. They all terminate finally in the peribronchial nodes.[2]

Most text books on general pathology discuss the process of anthracosis, but they do not enter into a description of the steps by which the condition develops. We have based our conception on the study of a great many lungs in the various stages of the anthracotic condition, and a description of the appearances of lungs in these various stages will serve to explain how we reached our conclusions. The finding of free carbon particles in the alveolar spaces was unusual, though in some of the very advanced cases black pigment masses filled some of the alveoli in such a way as to resemble a complete cast. In the early stages of the anthracotic process, the condition was manifested only by the presence within the air sacs of large round mononuclear phagocytes filled with carbon pigment, while in the slightly more advanced stages these cells were not only present in the alveoli but were also found in the interalveolar lymph spaces, in lymphatics of the interlobular septa, in those about the vessels, and beneath the pleura, and in those of the lower layers of the bronchial mucosæ. A little later these cells were found gathered in nests of considerable size, and many of them were seen to be compressed into spindles so that only the elongated nests of granules were visible. The very advanced conditions consisted only of a quantitative increase in all of the features mentioned above and if one examines a lung in a late stage of anthracosis, such as we have commonly observed in Pittsburgh, the following points will be noted: The deep layers of the bronchial mucosa may or may not show pigment bearing cells, and when they are present they are generally grouped about the small mucosal vessels. The alveoli contain pigment casts, pigment bearing phagocytes and rarely free pigment particles. The phagocytes are found in the lymph spaces between the alveoli, about the vessels, in the septa, and beneath the pleura, and those about the vessels are so numerous as to form rosette-like nodules consisting of alternate layers of pigment cells and of connective tissue trabeculæ (Figs. 1 and 7). The amount of connective tissue may be out of proportion to the number of pigment cells present. The striking point in the whole picture is the extensive plugging and obliteration of the small and medium sized lymphatics and the compression of the large ones. In the pleura and in the peribronchial lymph nodes the picture is a similar one, and in the latter the lymphoid tissue is often completely replaced by a scar tissue the meshes of which are full of pigment spindles. By following the findings from stage to stage, the process appears to consist in the taking up of the carbon pigment by cells in the lung alveoli and its transportation through the lymph spaces and channels to the peribronchial lymph nodes. During the process of transportation many of the pigment cells appear to be caught in the lymph spaces causing a backing up of similar cells in the spaces behind them. Here the cells seem to act as irritants and cause the proliferation of connective tissue, which holds them firmly. The nodules appear to be formed by the alternate blocking of small perivascular lymph spaces by pigment bearing cells and the formation of new spaces about the outside of the occluded ones. The new spaces then seem to become obstructed by the pigment cells in a similar way and so on until the concentric nodular anthracotic rosette is formed. The cells nearest the center are always more flattened and spindle shaped than those in the periphery. The continuation of the process over a long period of time leads gradually to a very severe embarrassment of the lymphatic drainage of the lung. It seems well to observe here that the separation of anthracosis by some authors into diffuse and nodular forms is one of degree only, as the condition which is diffuse in the early stages becomes nodular in the later forms.

Four very interesting questions arise in connection with the anthracotic process which we have up to the present purposely omitted from the discussion, because they seemed to be sufficiently important to deserve consideration under separate headings.

1. The question of the part played by the alveolar epithelium in the phagocytosis of pigment. Several authors state that the epithelial cells of the lung take up anthracotic pigment and that the pigment bearing cell is merely a desquamated alveolar lining cell. The author devised a combined staining method based on Heidenhain's hematoxylin as a nuclear stain, in combination with Mallory's aniline blue connective tissue method, which brought out the epithelial lining cells of the alveoli as clearly defined cells with red protoplasm and dark brown nuclei, resting upon a pale blue basement membrane. This stain was applied to sections from two hundred anthracotic lungs, and no pigment granules were found in the attached epithelial cells (Figs. 3, 4). After

they had become desquamated it was difficult to identify the epithelium from other mononuclear cells present, except in certain instances where the desquamation occurred in strips of several cells, attached end to end. In none of these instances were epithelial cells seen to contain pigment.

While not wishing to state definitely that epithelial cells cannot and do not take up pigment under some conditions we have no hesitation in saying that it is not the usual procedure and that we must look to other sources for the identity of the common pigment phagocyte.

2. Concerning the question of the identity of the pigment phagocyte. Beitzke[3] says that the pigment phagocyte is sometimes derived from the alveolar epithelium and at others is a wandering mononuclear white cell from the blood. Other authors have described them as endothelial leucocytes, those cells formerly called transitional and large mononuclear leucocytes which have been shown to come from the endothelial lining of the blood and lymph spaces.[4] We were able to get no specific stain to definitely settle this point. However, the pigment phagocyte observed in the alveolus and the endothelial leucocyte have many points in common. They are identical in size and appearance, they are both phagocytic, for blood pigment as well as coal pigment, they both take up all kinds of cells and cellular débris and lastly we will show later that the pigment phagocyte and the early cell of the tubercle, which we believe to be an endothelial cell, is one and the same cell.

By injecting pigment, in the form of Higgin's India ink, diluted one in five with normal saline we have attempted to determine the identity of the cells which acted as phagocytes.

Experiment III. — Guinea-pig 2. Two cubic centimeters of dilute India ink was injected beneath the scapula at 5 P.M. The animal was found dead at 8:30 A.M. on the following morning, and presented the appearance of having died some hours before. Macroscopic description: The subscapular region was found much blackened and the neighboring lymphatics were deeply injected with black pigment. Microscopic description: In the sections many polymorphonuclear leucocytes were present in the region and a few of them contained a scant number of granules of pigment. A relatively few endothelial leucocytes were present, but all of them contained abundant granules.

Experiment IV. — A similar dilute ink injection was made into the interstitial tissues of the abdominal walls of a guinea-pig. The animal was autopsied at the end of twenty-four hours. Macroscopic description: There was present in the tissues of the abdominal wall a localized nodule of swollen, edematous, and blackened tissue from which both smears and sections were made. Microscopic description: Both smears and sections showed a considerable number of endothelial leucocytes, and all of them contained a great number of pigment granules. There was a very marked polymorphonuclear leucocytic exudate present, but only occasional ones were found containing pigment granules (Fig. 6).

Experiment V. — This experiment was similar to the preceding, save that the injection was repeated at the end of twenty-four hours, and the animal was examined at the end of forty-eight hours. Macroscopic description: The gross appearance of the abdominal wall was similar to that in the preceding experiment. Microscopic description: A severe local endothelial leucocytosis was shown in the sections and most of these cells contained pigment. Many polymorphonuclear leucocytes were also present, but the phagocytosis of the pigment by these cells was insignificant.

It appears from these experiments that the polynuclear leucocytes may take up pigment, but that their action is transient and unimportant, while the observations point to the endothelial leucocyte as the chief pigment phagocyte of the body.

3. The length of time during which the enclosed pigment remains intracellular is very important. As we have described above the pigment bearing cells often become caught in the lymph spaces and when they have been surrounded by scar tissue appear simply as pigment spindles and look like nests of free granules, or as if they were incorporated in spindle shaped connective tissue cells (Fig. 7). In acute inflammation of the lung, and more particularly in edema, the spindles again assume a more or less round or oval form (Fig. 8), suggesting that the spindle shape is due entirely to the pressure of the scar tissue. In two experiments we were able to reproduce the condition.

Experiment VI. — A small amount of dilute India ink was injected interstitially into the ear of a rabbit. At the end of twenty-six days sections were made. Almost all of the pigment had been taken up and was found in the form of spindles firmly fixed between strands of connective tissue (Fig. 9).

Experiment VII. — The ear of another rabbit was treated in a similar way. After forty days the ear was dipped into water at 60° C. for three minutes. At the end of fifteen hours a very extensive edema of the ear had developed and the animal was brought to autopsy. Sections showed a very extensive serous interstitial exudate without any cellular elements to separate the strands of connective tissue very widely. Almost all of the pigment was found to be present in cells which were of the large round type (Fig. 10).

In some processes within the lung, such as abscess, gangrene, the various granulomata, and tumors, which are accompanied by necrosis, the anthracotic pigment is found extracellular and is seen widely distributed as free granules. These granules sometimes remain free in caseous areas, or in scar tissue, or they may again be engulfed by large mononuclear phagocytes. From our own observations we feel justified in saying that carbon pigment once taken up by the cells remains intracellular indefinitely unless freed by some process producing general necrosis of the tissues.

4. How long do phagocytic cells remain free in the alveoli? There is at present no accurate means of determining the length of time during which a cell may remain free in the alveolus, though there are several points which indicate that this is longer than is generally supposed. One may observe many cells in the lung alveoli which are only partially filled with pigment, but to find such a one in the intra-alveolar lymph spaces is quite unusual. This suggests that the phagocytic cells are generally pretty well loaded when they leave the alveoli.

In pneumonia and edema of the lung where individuals have been confined to the hospitals for some time and presumably not inhaling very much pigment, the alveoli often contain numerous pigment bearing phagocytes. The almost constant presence in the alveolar spaces of "Herzfehler Zellen" in brown induration of the lung is hardly a terminal condition, and establishes further evidence that phagocytic cells may remain free in the alveoli for a considerable length of time. In Experiment II. we found that although the soot inhalations had been carried on for eighty-seven days, pigment bearing cells were found only in the alveoli and inter-alveolar spaces and there was no evidence that any had migrated as far as the large lymphatics. All of these points seem to indicate that the phagocytic cells are not transient scavengers, but in a more leisurely manner gather their pigment-load and transport it to the tissue spaces.

Summarizing the foregoing work we conclude:

1. The quantity of pigment taken up by the upper air passages is a negligible one.

2. The lining cells of the lung alveoli take little or no active part in the phagocytosis of carbon pigment.

3. The process consists in the phagocytosis of the pigment within the lung alveolus by a cell, which is probably an endothelial leucocyte. This cell then passes into the pulmonary lymphatics where it sometimes lodges and becomes surrounded by connective tissue. The pigment remains intracellular until acted upon by some process producing a local necrosis of the tissues.

4. The importance of the sequence of the process lies in the fact that the lymphatics of the lung become obliterated either mechanically or by fibrosis.

II. The association of anthracosis and tuberculosis. — Pulmonary tuberculosis in adult individuals in Pittsburgh is constantly associated with more or less anthracosis, so that ample opportunity was afforded for the study of the effect of the one upon the other. The important lesion of tuberculosis is the tuberculous granuloma or "tubercle," and the following discussion is confined to a consideration of the related lesions of this characteristic tuberculous lesion, and anthracosis.

The present day knowledge of the histogenesis of the tubercle is the result of the accumulated work of more than a generation of pathologists. Point by point has been added year by year, and credit cannot be given to any single individual or group of individuals, and more especially is this true for the reason that our facts are still deficient in certain details. The names of Baumgarten[5] working in Germany and of Borrel[6] in France, however, stand out prominently among the founders of the experimental studies, to which we owe so much. The formation of the tubercle as we understand it at present, seems, in general, to occur in the following way:

When tubercle bacilli enter the smaller vessels or lymph spaces they are shortly incorporated by the cells lining these structures. In both vessels and lymph spaces the process appears the same so that the description of the former will suffice. The cells which have taken up the tubercle bacilli undergo rapid proliferation and develop a nest of proliferated endothelial cells which tends to fill the vessel, obliterate it, cut off the nutrient supply to the nest, and leave it an extravascular structure. The endothelial cells have by this time changed their morphology and somewhat resemble epithelial cells, for which reason they have long been known as "epithelioid" cells. About this time a few polymorphonuclear leucocytes may frequently be seen in the margins of the structure, but, in the later stages, lymphocytes alone are present. The next change which is usually observed is the appearance, near the center of the nest, of a multinucleated or giant cell, which was described by Langhans in his early studies on tuberculosis and to which his name has been given. That the Langhans' giant cell is the product of the endothelial cell seems now to be unquestionable, but a considerable dispute still exists as to whether it arises by a fusion of the endothelial cells or by a division of the nucleus without a multiplication of the cell. Caseation necrosis is next seen near the center of the nest and commonly first manifests itself in the center of the giant cell. With the appearance of caseation there is not uncommonly a proliferation of connective tissue about the margin which is an attempt on the part of the tissues to encapsulate the lesion. This completes the structure of the miliary tubercle (Fig. 15). Complete encapsulation and healing may follow with more or less absorption of the necrotic matter by the tissues or the deposit of calcium salts within the caseated areas. On the other hand a local or general spread of the tuberculous process may follow. A certain amount of local invasion from the original tubercle may take place by direct extension leading to the development of numerous closely aggregated and fused tubercles. The lesion thus produced is known as a conglomerate tubercle. A more extensive local spread, even to the involvement of an entire organ, often takes place by way of the anastomosing lymph spaces.

Recently, considerable evidence has been advanced to show that the so-called epithelioid cells are at all times endothelial cells, and if this is true the term "epithelioid," which is somewhat confusing, should be discontinued. Mallory has called attention to the constant involvement of endothelial cells in the earliest recognizable lesions of tuberculosis, and has shown that no fibrils are demonstrable by stains in the tubercles until the stage of encapsulation is reached, at which time fibrils appear in conjunction with the proliferating connective tissue cells in the outer border. Since endothelial cells are not known to produce fibrils, the evidence is in favor of the essential cell of the tubercle being endothelial in character. Bowam, Winternitz, and Evans have shown experimentally that tubercles may be developed in the liver from the Kupffer stellate cells, which are also considered as endothelial cells. By first inducing a vital staining of these cells in animals by injecting trypan blue into the circulation, then inoculating the same animal with tubercle bacilli, they were able to follow the formation of tubercles by the stained cells. I have also induced the development of tubercles experimentally, the essential cells of which were phagocytic both for pigment granules and the tubercle bacillus (Experiments VIII., IX., and X., and Figs 17, 18, and 19), and if we are right in concluding that the endothelial cell is the general pigment phagocyte of the body, we have another link in the chain which identifies the "epithelioid" as an endothelial cell.

As to the nature of the Langhans' giant cell we have, in several instances, observed multinucleated cells containing both pigment granules and tubercle bacilli. This would indicate that the cells exhibiting the phagocytic properties to foreign particles and tubercle bacilli were of the same origin and that the giant cells were but a morphological modification of these. As to the way in which the phenomenon of multinucleation occurs we have no conclusive additional evidence. An experiment was planned by which it was hoped to discover a constant ratio between the amount of pigment taken up and the number of nuclei present in the giant cell. The experiment failed, firstly, because time was not allowed for complete or nearly complete phagocytosis of the pigment before the tubercle bacilli were introduced and, secondly, because the amount of pigment used was so great as to completely obscure many of the nuclei in the cells. The experiment though unsuccessful seems worthy of repetition.

Lesions illustrating the association of the various stages of tubercle formation with all degrees of anthracosis were found in the materials secured from the autopsies and the following interesting observations were made: (1) Examples of early tubercles were found which consisted of simple nests of endothelial cells, some of which contained black pigment granules though they differed apparently in no other way (Fig. 16). (2) Pigment granules were found in many of the giant cells, and when caseation necrosis was also present in these cells the nuclei were found arranged in the periphery with the pigment granules grouped in circles about them (Fig. 20). (3) In tubercles where caseation was advanced much of the pigment was found to have been liberated and occurred either as free granules diffusely distributed throughout the necrotic foci or, as was more often the case, gathered in the margins of the caseous areas where it was found undergoing a second phagocytosis by endothelial cells (Fig. 21). (4) Many partially and completely encapsulated tubercles were seen with great numbers of pigment spindles caught in the meshes of the capsules, and in these instances the connective tissue was unusually abundant. Obliteration of the neighboring perivascular lymph spaces by anthracotic fibrosis was a common additional finding in some of these lesions.

The number of cases examined was too small to allow the drawing of a general conclusion, but it seemed that there was less local spread and more extensive fibrosis in this latter type with anthracosis than is usual in ordinary pulmonary tuberculosis. It further seemed that the presence of pigment within the endothelial cells did not interfere with their development of typical tubercles (Experiments VIII., IX., and X.).

Experiment VIII. — Two cubic centimeters of a very dilute suspension of India ink was shaken up in normal salt solution with two loops of bacillus tuberculosis bovinus (kindly furnished by Dr. W. L. Holman) and was injected into the deep muscles of the thigh. After twenty-four days the animal was killed with chloroform and autopsied. Macroscopic description: Indefinite grayish-black tubercle-like nodules were found among the muscle fibers, and some of the intermuscular lymph spaces appeared as blackened lines. There was no evidence of involvement of the inguinal nodes, nor of the other organs or tissues of the body. Microscopic description: Many early tubercles were seen in the process of formation and the cells composing them often contained black pigment granules (Fig. 17). Tubercle bacilli and these pigment granules were repeatedly found in the same cells. Relatively few multinucleated cells were seen, but in some of them bacilli and pigment granules were found together. Practically no fibrous proliferation was present about the lesions and the cells did not show any kind of fibrils when special stains were applied.

Experiment IX. — One cubic centimeter of a 1 in 5 suspension of India ink in normal saline was shaken up with two loops of bovine tubercle bacilli and injected underneath the scapula of a rabbit. Ten days later inhalations of soot similar to those used in Experiment II. were begun. These were carried out about every five days and about fifteen inhalations were given. After seventy-four days the animal died from general tuberculosis. Macroscopic description: A large caseous mass about 4 centimeters in diameter near the center of which was a small black nodule was found beneath the scapula. The lungs, liver, spleen, and kidneys showed very advanced caseous tuberculous lesions. A few rather indefinite black granules appeared about the margins of the lung tuberces. Microscopic description: The lungs alone are of interest in this experiment. They contained all stages of tuberculous lesions, and a few fine pigment granules were observed in some of the cells forming the tubercle. Two vascular lesions were of interest because they showed direct extension of early tubercles into the lumina of vessels without causing rupture of the walls. The subscapular lesion was in a very advanced stage of caseation necrosis and was valuless for study.

Experiment X. — Injections as carried out in Experiment VIII. were made into the interstitial tissue of a rabbit's ear. The animal was brought to autopsy at the end of twenty-six days. Macroscopic description: The ear showed one large diffuse black area involving approximately one-half of the ear. The tissues were somewhat thickened and contained three large and several small grayish-black nodules. At the base of the ear was found an enlarged and blackened lymph node. Microscopic description: Sections of the ear and lymph node both demonstrated the presence of early tubercles, with black pigment granules in the cells of the tubercle, and in both instances tubercle bacilli and pigment granules were found in the same cells (Fig. 19).

In all three of these experiments we were able to induce miliary tubercles formed by cells which were filled with pigment granules. This indicated that the presence of pigment in the specific cells did not exert any inhibitory influence to the development of tubercles. By demonstrating pigment granules and bacilli in the same cells of the tubercle, we were able to show that a single cell may actively phagocyte both materials. In other words, the essential cell of the tubercle and the pigment phagocyte were found to be identical. Still more interesting was the finding in Experiment X. in which both the pigment phagocytes and tubercle forming cells were found in a neighboring lymph node, where tubercles were being formed by cells which contained pigment.

Summing up our observations on the associated lesions of anthracosis and tuberculosis we came to four conclusions:

1. The cell which takes the early active part in the formation of a tubercle is phagocytic for tubercle bacilli and for pigment granules and is probably an endothelial cell.

2. The presence of pigment granules within these cells does not interfere with the cells taking part in the formation of a tubercle, in the usual way.

3. The presence of pigment-bearing cells in the connective tissue about tuberculous lesions acts as an additional stimulus to fibrosis and encapsulation.

4. The obliteration of the pulmonary lymph spaces in the

anthracotic process is unfavorable for the local spread of tuberculosis, and aids in the localization of the condition.

III The association of pneumonia and anthracosis.— With pneumonia the relation of anthracosis is a very different one. The process is one of acute inflammation wherein the alveoli, bronchioles, and often the smaller bronchi become filled with a fibrino-purulent exudate. Ordinarily this exudate remains in the alveoli for a relatively short time, usually from five to nine days, and then undergoes resolution. The process of resolution consists, firstly, in a softening and liquefaction of the exudate, which takes place through the autolytic action of the different elements, and is known as puriform softening, and secondly, in getting rid of the resulting débris. Much of the resolved exudate is coughed up, but the greater part of it passes back into the circulation by way of the lymph spaces and through the lymph nodes.[7] During resolution these spaces are found to be dilated and to contain fluid, fragments of fibrin and many types of exudative cells. Among these cells are numerous phagocytes containing other cells, cell débris, fibrin, and fat globules (Fig. 13). The contents of the sinuses of the lymph nodes is exactly the same (Fig. 12). It is evident that for the removal of this débris as well as for active phagocytosis comparatively large channels are necessary, and it is obvious that anything which may impede the passage through the lymphatics must interfere with the healing process. The mechanical blocking of the spaces forces the débris to find other channels of exit, and the imperfect drainage leads to the accumulation of waste products which, in turn, may retard the activity of the proteolytic enzymes.

When for any reason resolution of pneumonia fails to take place the microscopic picture presents certain characteristics. The cellular elements of the exudate are not numerous and are often lymphocytic; the fibrin becomes contracted into firm hyaline, spindle, or fan-shaped masses which are bathed in fluid, and the alveolar wall appears thickened and edematous. At somewhat later periods these fibrinous masses occasionally undergo organization in a way comparable to the repair of a wound. Abscesses are also very common findings in pneumonic lungs where failure of resolution has occurred, and gangrene is also seen in some instances. Not only are such lungs unusually susceptible to secondary infection, but the actual presence of the undigested fibrin is claimed to be extremely toxic.

Our evidence of the effects of anthracotic conditions on pneumonia was obtained by a microscopic study of sixty-two cases of the disease. Of these, thirty-eight were lobar, twenty were of the bronchial type, four were hypostatic, and two were the end result of general septicemia.

Of the thirty-eight lobar pneumonias, nine, or nearly twenty-five per cent, were diagnosed "unresolved" at autopsy and two others presented microscopical evidences of the same condition. Two of the bronchial type contained much hyaline fibrin and abscesses, and one of the hypostatic variety showed advanced organization.

This unusually large percentage of failures in resolution suggested a careful study of the pulmonary lymph spaces in these cases. This was carried out as far as we were able in the sections. Our attention was mainly directed toward the large channels because the small lymph spaces were obviously involved in all of the cases, and also because a severe involvement of the larger lymphatics indicated an extensive participation of the smaller contributory vessels over a considerable area. We found the large perivascular and subpleural lymph spaces closed or compressed in four cases by anthracotic fibrosis. Two cases presented a similar picture save that the amount of scar tissue seemed to be out of all proportion to the number of pigment cells. One instance was found where the lymph spaces were closed by scar tissue alone, and in two others there was no local evidence which could be construed as having anything to do with failure of resolution. The two remaining cases were pneumonias in which there were coexistent septicemias, and were omitted from consideration because the origin of the lung abscesses might have occurred as a part of the general process. Both of these lungs were examples of late stages of anthracosis. Our results, then, showed that in six of the nine cases of unresolved pneumonia the larger lymph channels were severely embarrassed by the anthracotic process.

The failure of resolution in pneumonia is commonly attributed to the low state of the general bodily condition, although Pratt[8] called attention to the frequency of delayed resolution in individuals who had been previously attacked, and attributed it to the fibrosis of the lymph spaces following the lymphangitis which occurs during resolution.

The results of the microscopic examination of the lymphatics in the total number of lobar pneumonias were as follows: Eighteen cases presented dilated lymph spaces filled with serous or sero-purulent exudate; five were closed by acute fibrino-purulent exudate, nine were practically obliterated by anthracosis; two were obliterated by scar tissue, and four were in the stage of resolution with large numbers of phagocytes in the lymph sinuses.

An analysis of these findings seems to indicate that during an attack of pneumonia in an otherwise normal lung the lymph vessels are generally engaged in an active exchange of fluids. Even in those instances where these channels are filled with a fibrino-purulent exudate this exudate has a better chance of becoming liquefied and returning to the circulation than a similar exudate in the alveoli. So that even under these circumstances they would again be available for drainage.

The presence of the phagocytes in the channels and in the sinuses of the lymph nodes shows fairly conclusively that the lymphatics are important drains during the stages of resolution of pneumonia, and if these are closed the waste products of autolysis of the exudate must accumulate, and such an accumulation undoubtedly interferes with proper enzymatic action. In several of the above mentioned cases where the lymphatics were found to be closed, death occurred before the stage of resolution was reached. It is, of course, impossible to say that the presence of the anthracotic condition had any definite connection with the fatal result. Yet it is likely that the lymphatics in inflamed areas are just as important for the entrance of fresh fluids as for the exit of waste materials. It has been variously shown that the cultures of pneumococci obtained from pneumonic lungs after crises are less virulent than those made in the early stages, and this suggests some immune reaction against the organisms. If we are correct in the supposition that immune substances are the products of the entire body as well as of local origin, we must recognize the need of a constant influx of fresh fluid containing such immune products. It seems, then, that the closed lymph spaces may have had some effect even in this latter class of cases.

Our series although small seems to point toward a certain relation between "unresolved pneumonia" and anthracosis with chronic obliterating lymphangitis.

An interesting collateral finding, brought out by the newly devised staining method used in demonstrating alveolar epithelium, showed that desquamation of alveolar epithelium in pneumonia is inconstant and occurs only in some alveoli. Instances were observed in which the pneumonia had reached a stage of resolution and yet practically all of the alveolar epithelium was intact.

1. Any process which interferes with the free lymphatic drainage during pneumonia will delay resolution, both by actual mechanical obstruction to the migration of cells, and by aiding in the accumulation of waste products probably embarrassing enzymatic digestion of the exudate.
2. Anthracosis is an important process in the lung interfering with lymphatic drainage, and is a factor in causing delayed resolution.

Summarizing the various points indicating the disease importance of anthracosis which we have gathered from histological evidence we draw the following conclusions:

1. Moderate anthracosis in an otherwise normal lung is not in itself detrimental to health.
2. In tuberculosis and granulomatous conditions in which

the reactions are chiefly centered in focal lesions of the tissues, the anthracotic condition is either entirely passive, or is active in assisting healing, in that it is an additional stimulus to fibrosis and encapsulation and in that it aids in the localization of the process through the obliteration of the lymph spaces.

3. In acute inflammatory conditions where the lymphatics are important for proper resolution, anthracosis becomes seriously detrimental, because of the obliteration of these spaces.

[I wish to express my thanks to Dr. Oskar Klotz for his very able advice during the preparation of this paper and to Mr. William Coburn for his efficient aid in carrying out the experimental work.]

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DESCRIPTION OF PLATES XIV-XVIII.

Plate XIV., Fig. 1. — Perivascular arrangement of nodular anthracosis.

Fig. 2. — Subpleural type of anthracosis.

Fig. 3. — Alveolus containing many pigment phagocytes and a pneumonic exudate. Note the alveolar epithelium swollen and free from pigment.

Fig. 4. — Alveolus containing pigment phagocytes with alveolar epithelium intact. Note one cell containing both pigment and a red blood corpuscle.

Plate XV., Fig. 5. — Experimental anthracosis. Pigment phagocytes in alveoli and inter-alveolar lymph spaces.

Fig. 6. — Injection of carbon pigment in abdominal wall. Pigment present in large round cells and in inter-cellular spaces. Polynuclears contain no pigment.

Fig. 7. — Spindle-like arrangement of pigment in perivascular anthracotic nodules.

Fig. 8. — Effect of edema on spindle-like pigment occlusions in perivascular anthracosis.

Plate XVI., Fig. 9. — Experimental fibrosis produced by the injection of India ink into a rabbit's ear.

Fig. 10. — Effect of artificially produced edema on rabbit's ear which had been treated in a similar way to that seen in the preceding figure.

Fig. 11. — Alveoli containing pneumonic exudate in stage of resolution. Note epithelial cells intact on alveolar walls.

Fig. 12. — Lymph spaces of peribronchial lymph node containing phagocytes from preceding figure.

Plate XVII., Fig. 13. — Perivascular lymph space filled with broken up fibrin and phagocytes from same case as preceding figure.

Fig. 14. — Perivascular lymph spaces completely obliterated by carbon pigment and fibrosis. From severe case of unresolved pneumonia.

Fig. 15. — Formation of early lung tubercle.

Fig. 16. — Early tubercles containing pigment bearing cells (human).

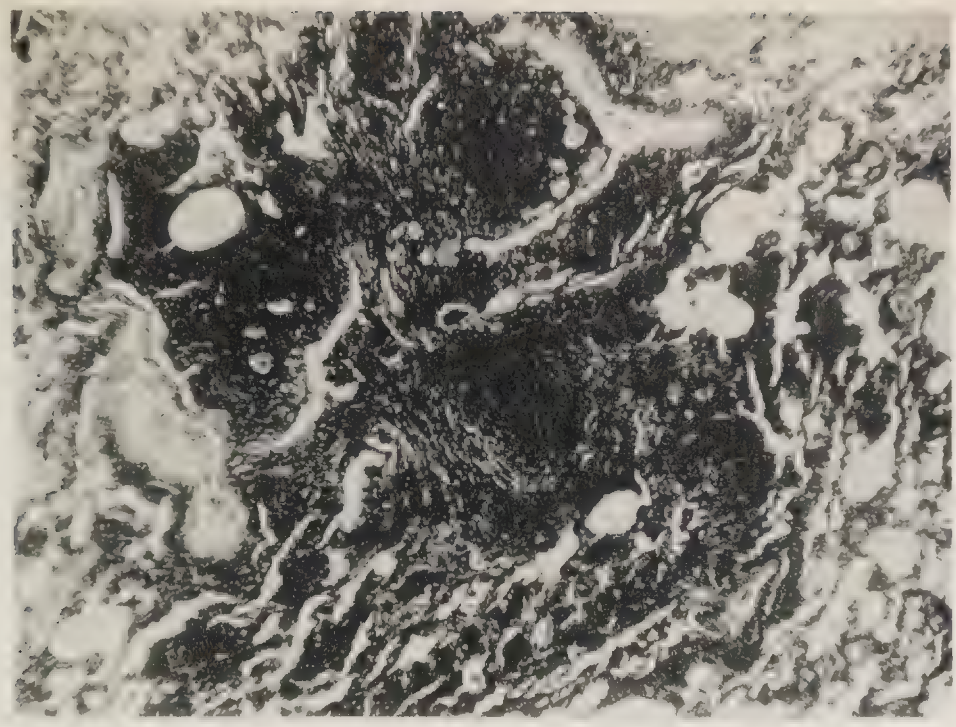
Fig. 17. — Experimental tubercle in rabbit's thigh. Pigment bearing cells actively forming the tubercle.

Plate XVIII., Fig. 18. — Oil immersion view of same tubercle. Cells contain both pigment granules and tubercle bacilli.

Fig. 19. — Tubercles containing pigment bearing cells in lymph node.

Fig. 20. — Arrangement of pigment in giant cells in late stage of tuberculosis.

Fig. 21. — Distribution of carbon pigment in the periphery of caseous tubercle.



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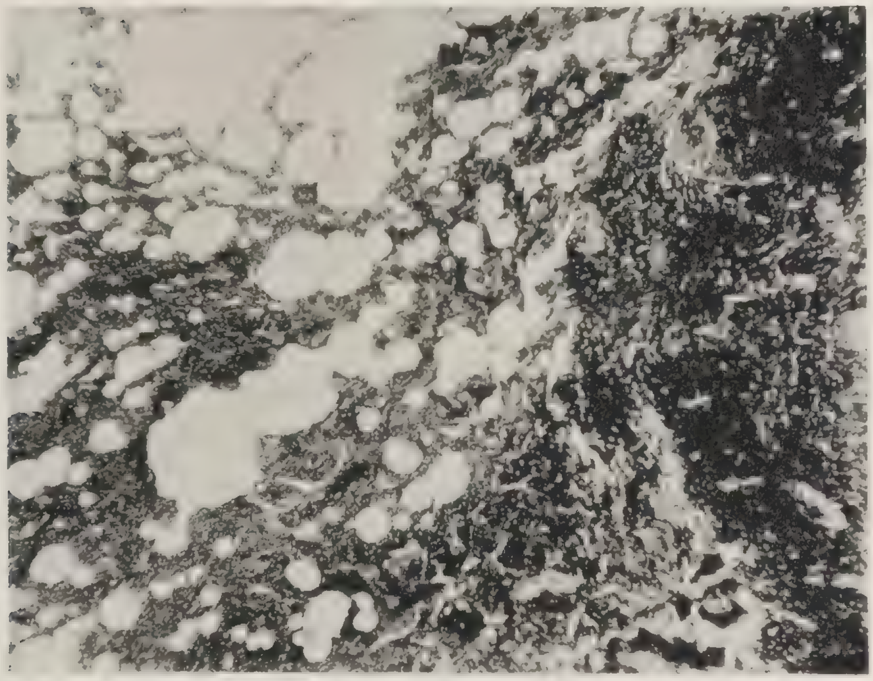

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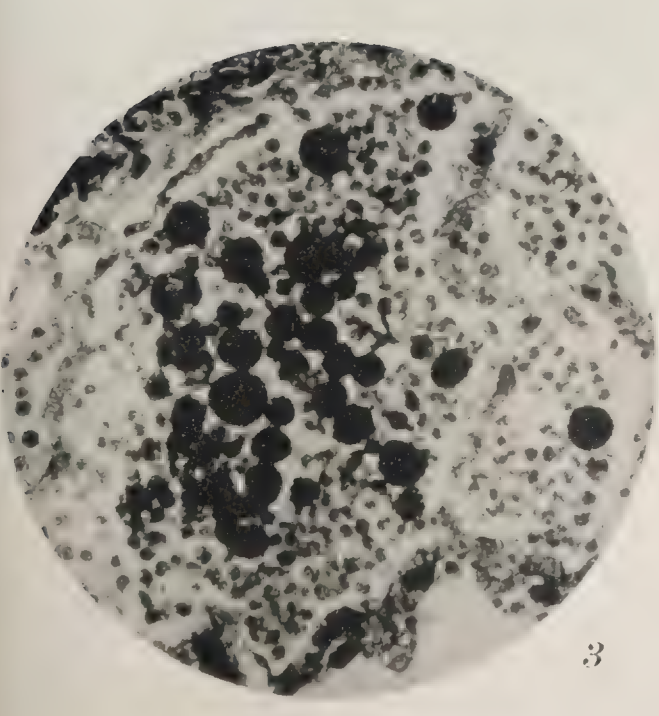

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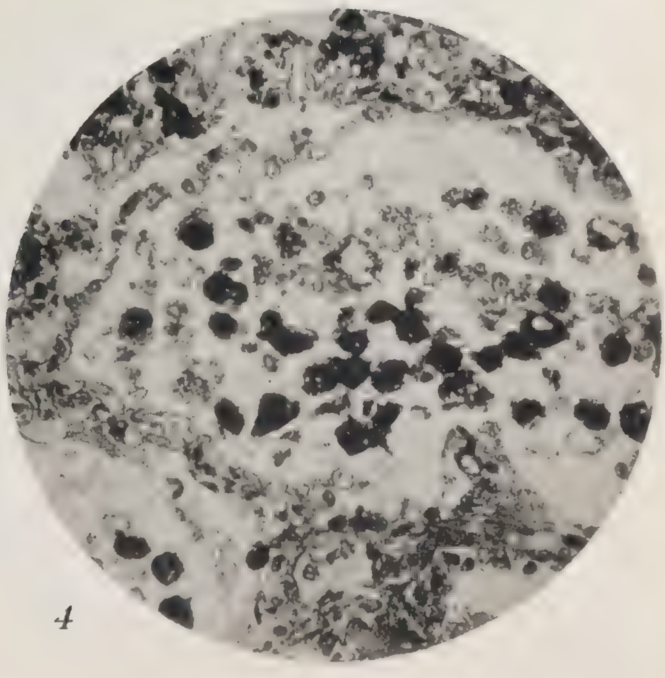

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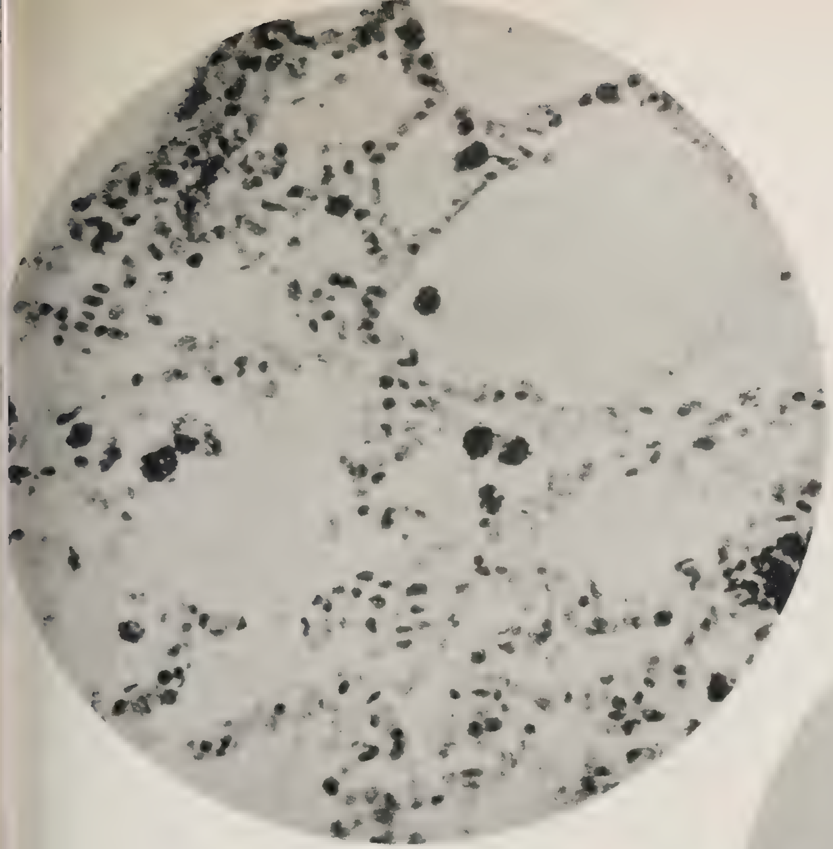

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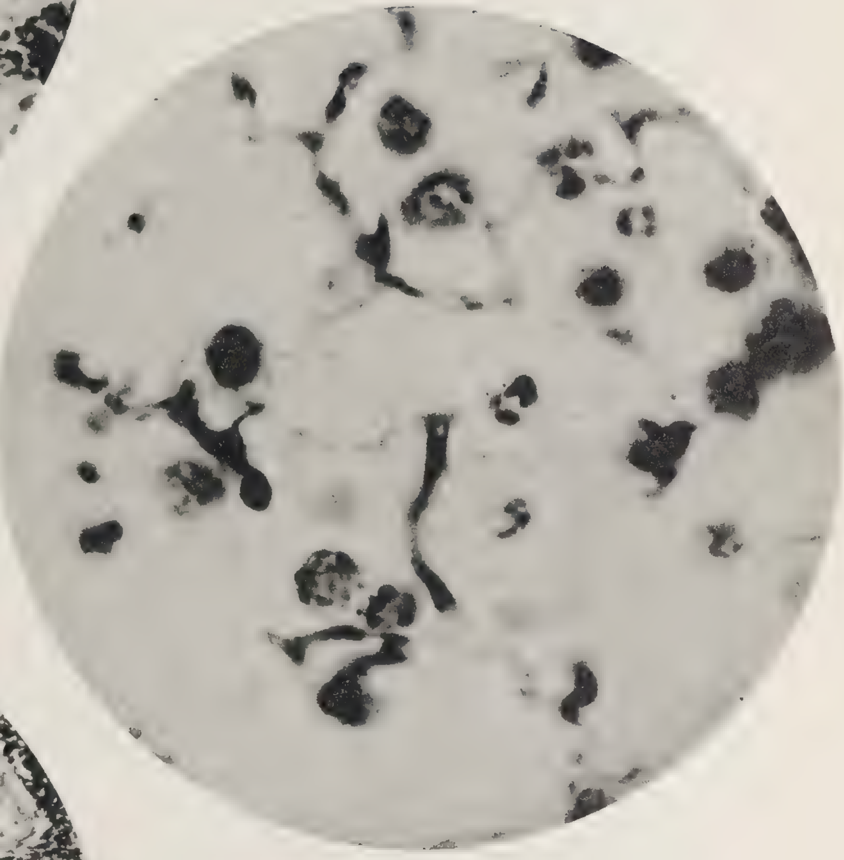

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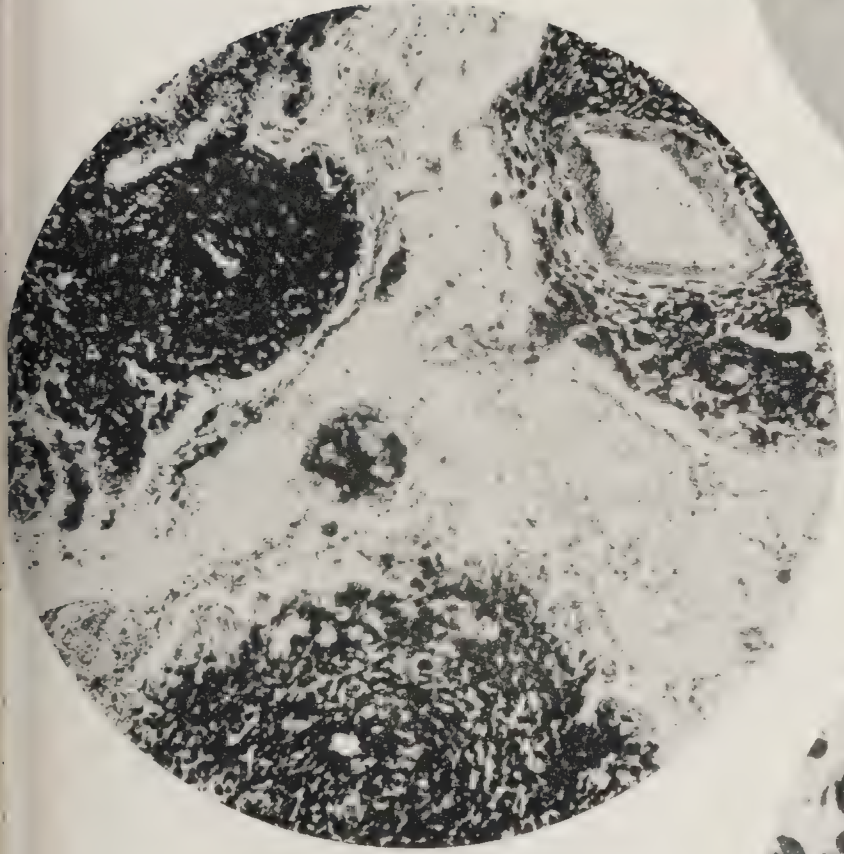

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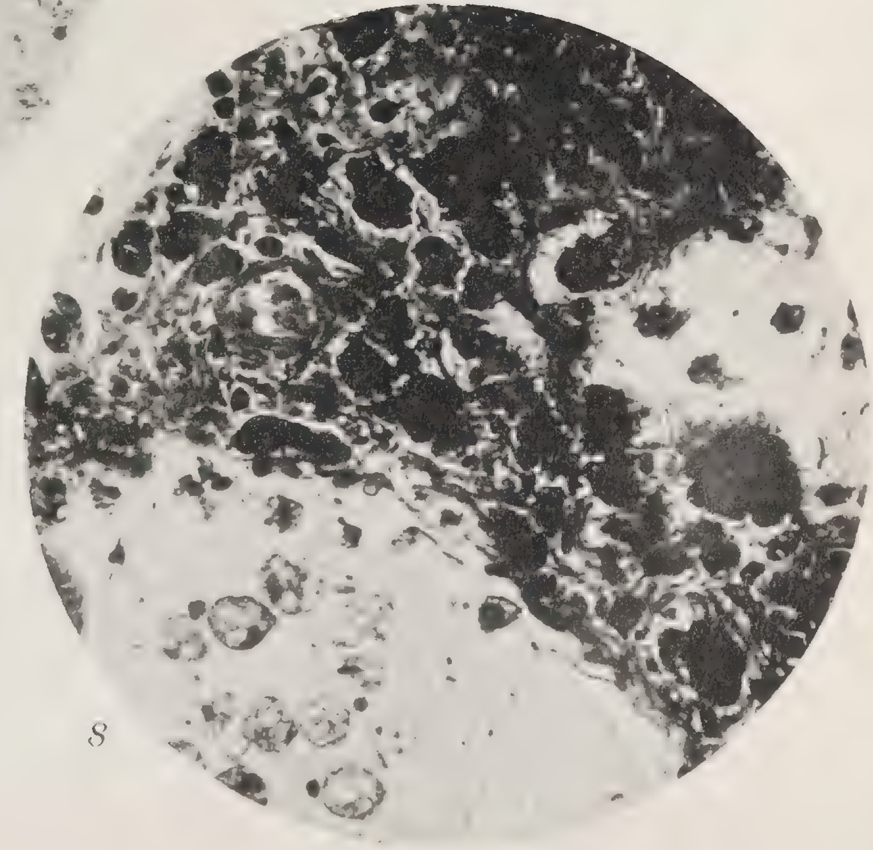

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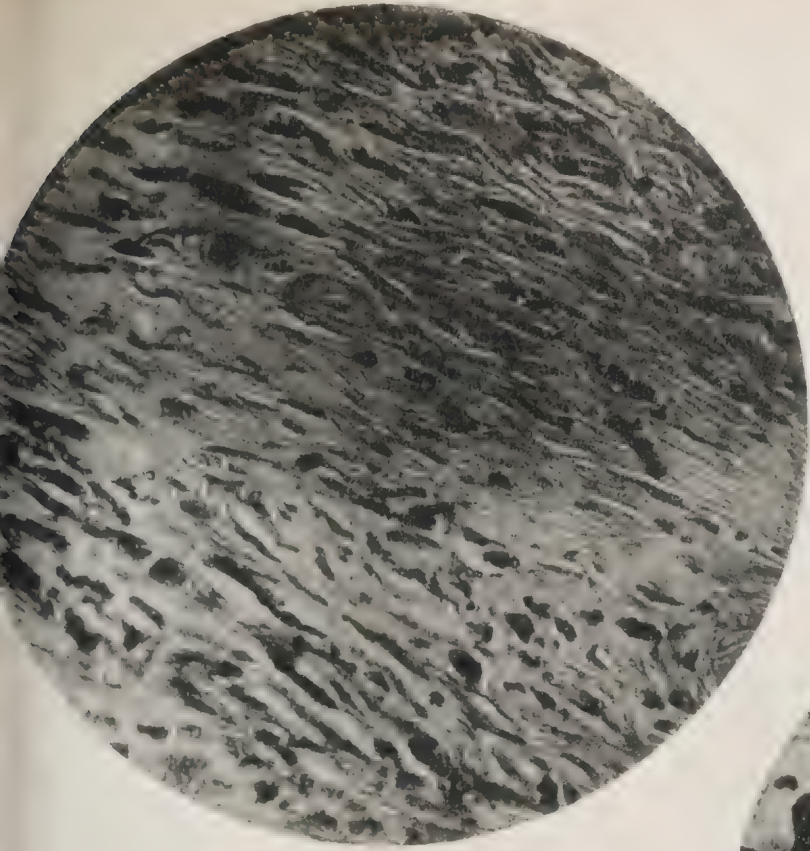

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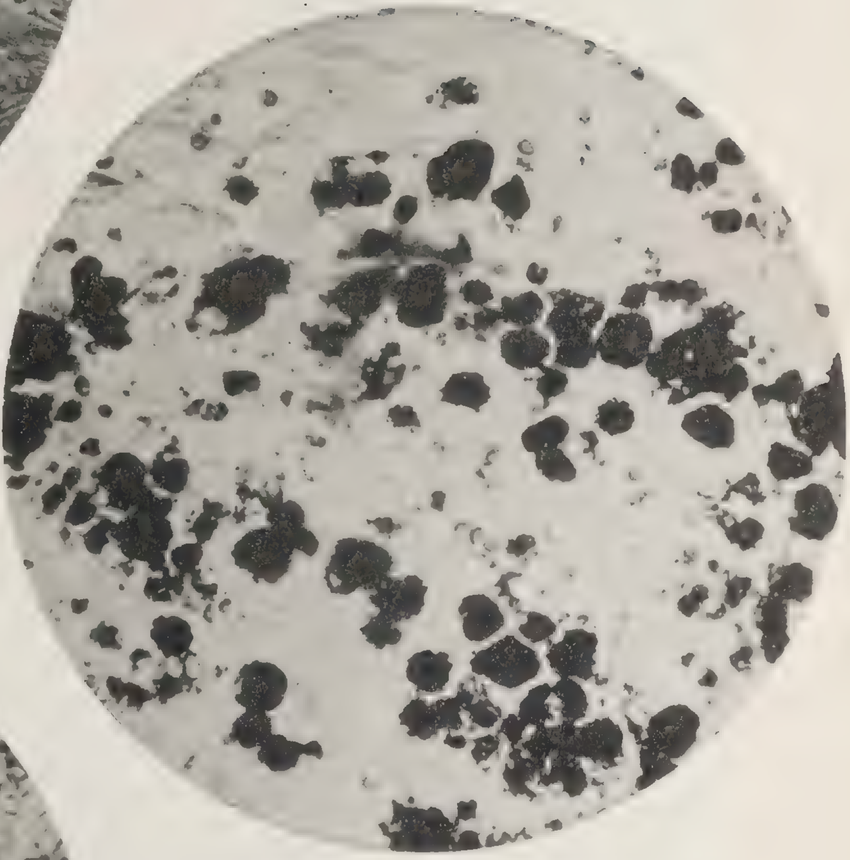

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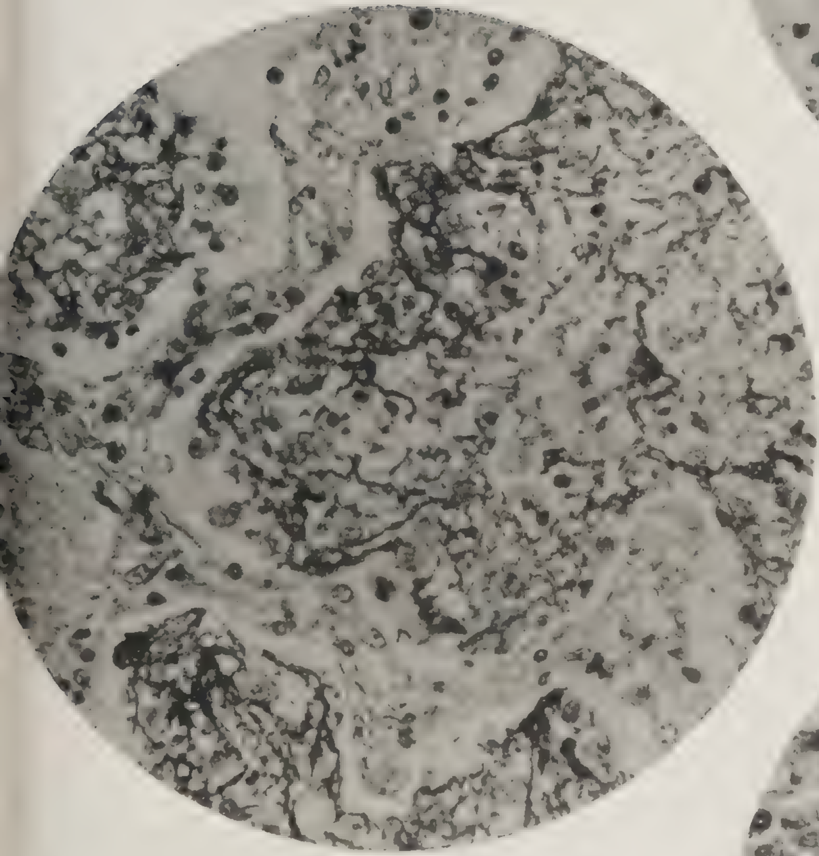

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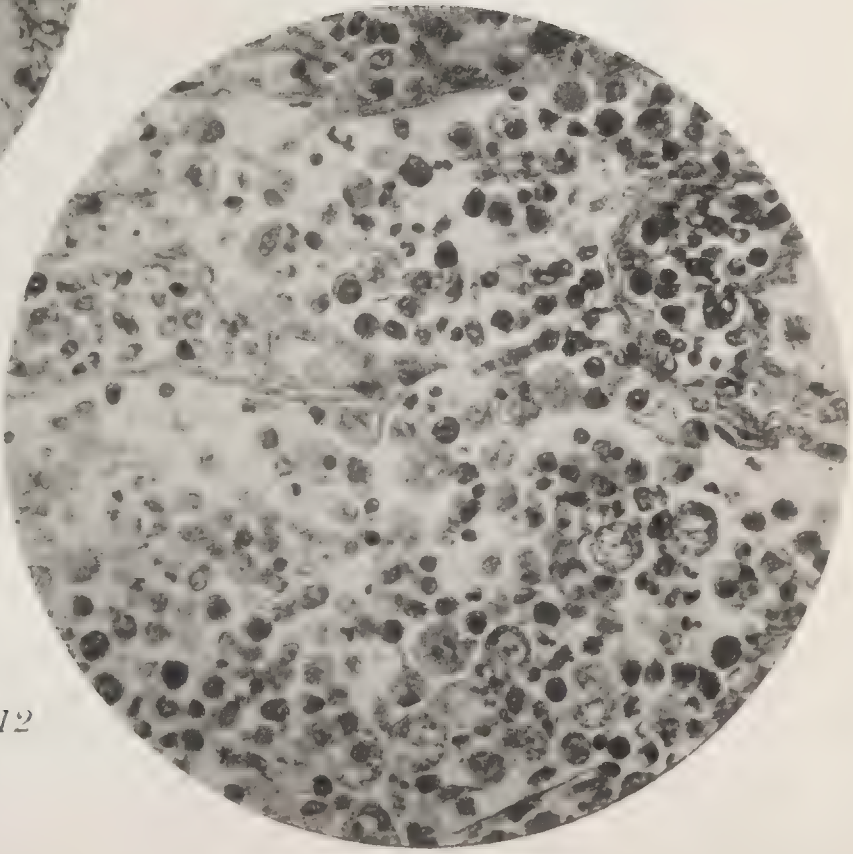

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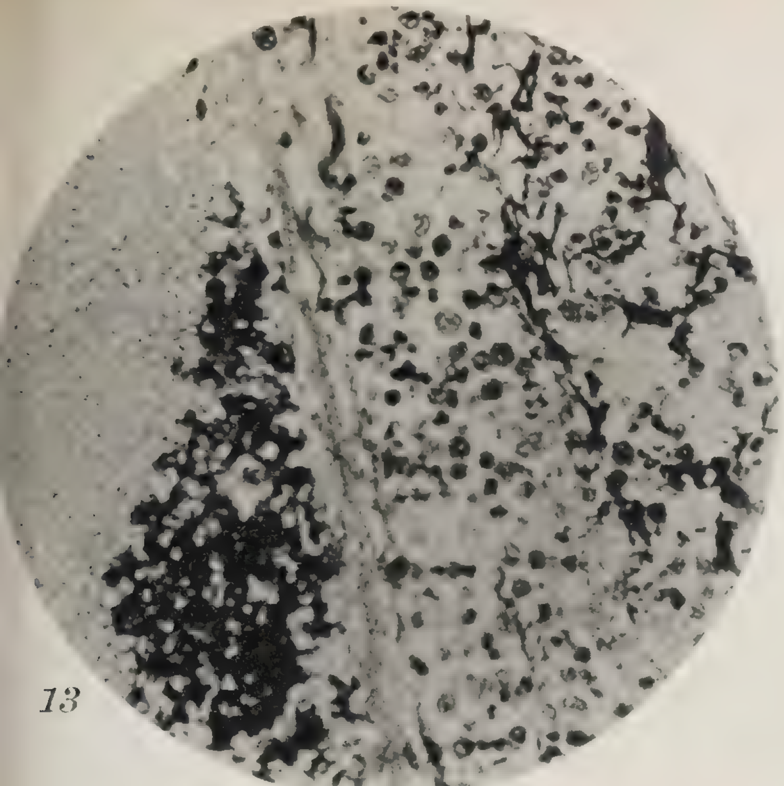
Haythorn Pulmonary Anthracosis



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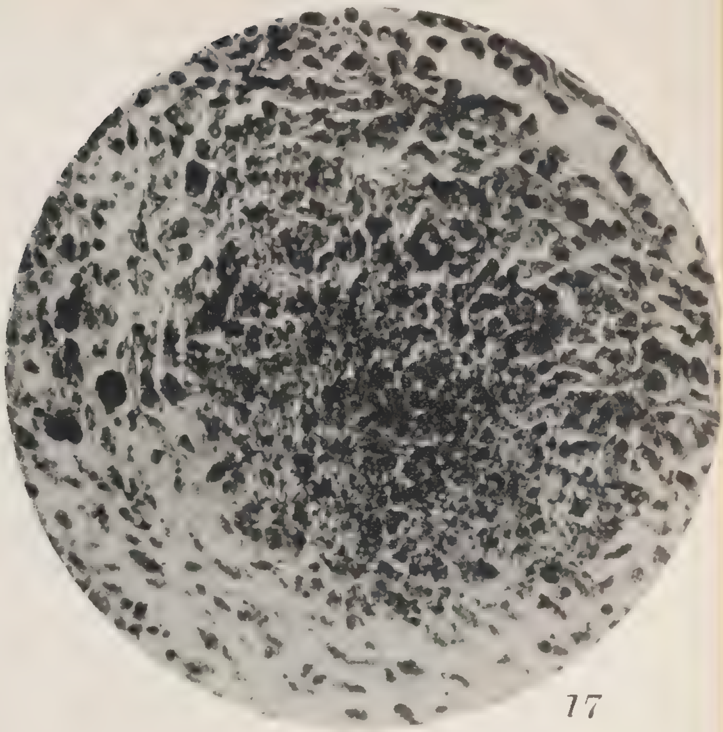

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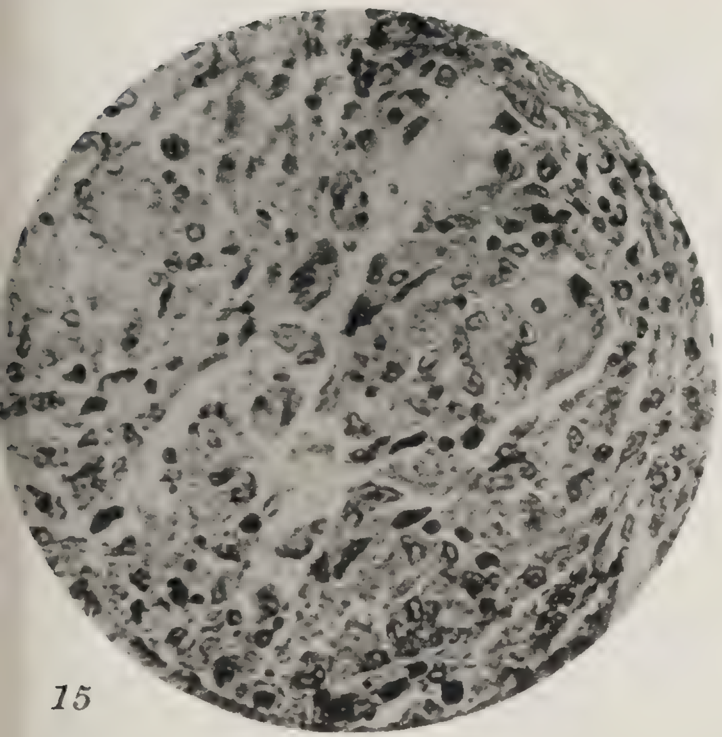

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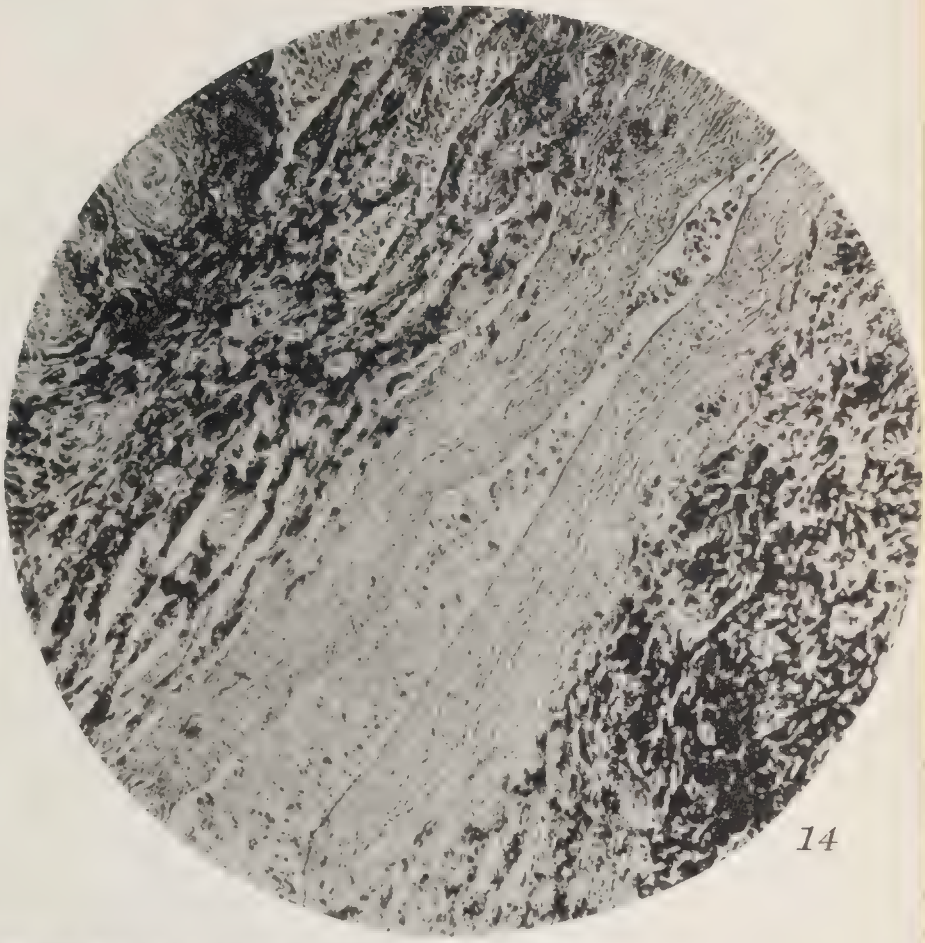

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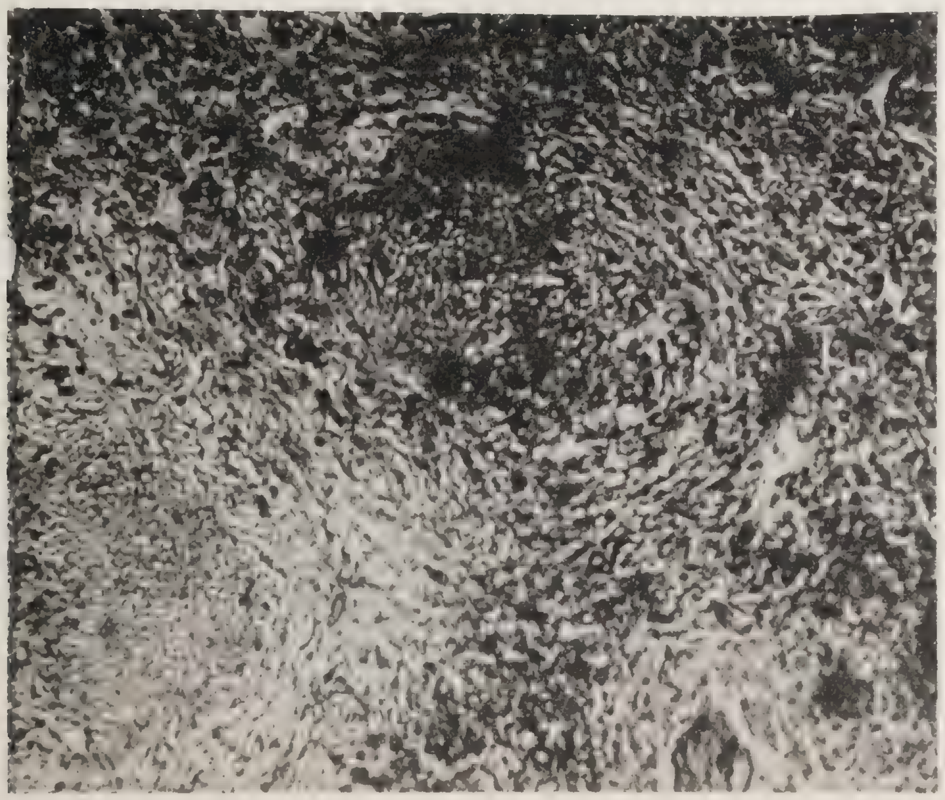

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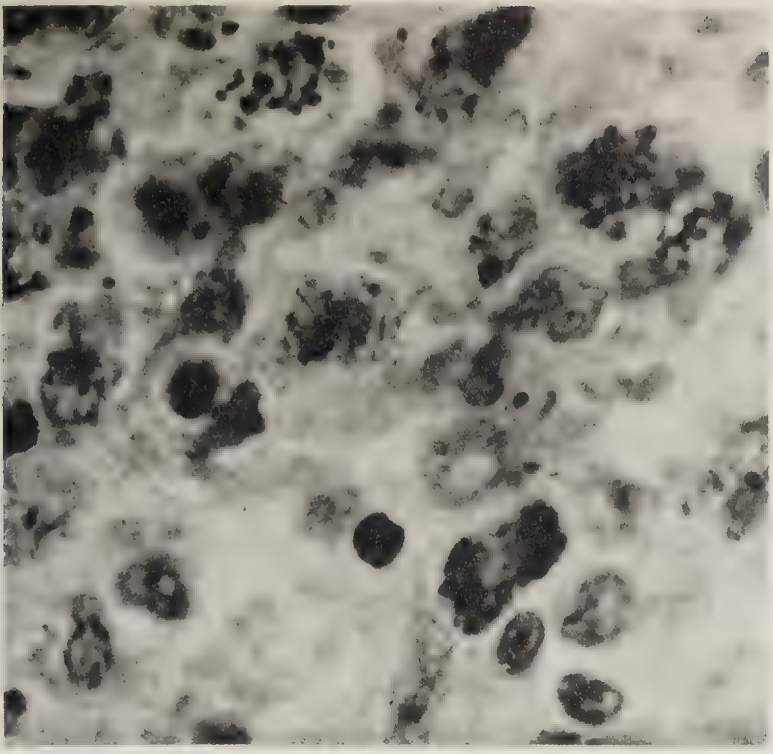

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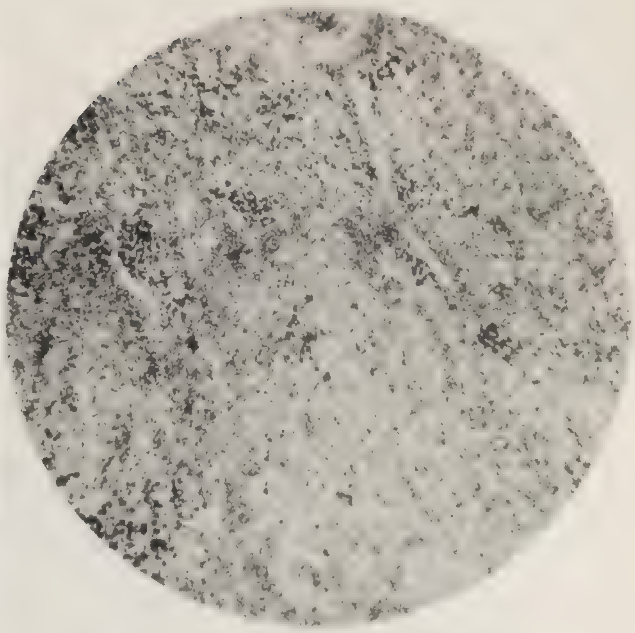

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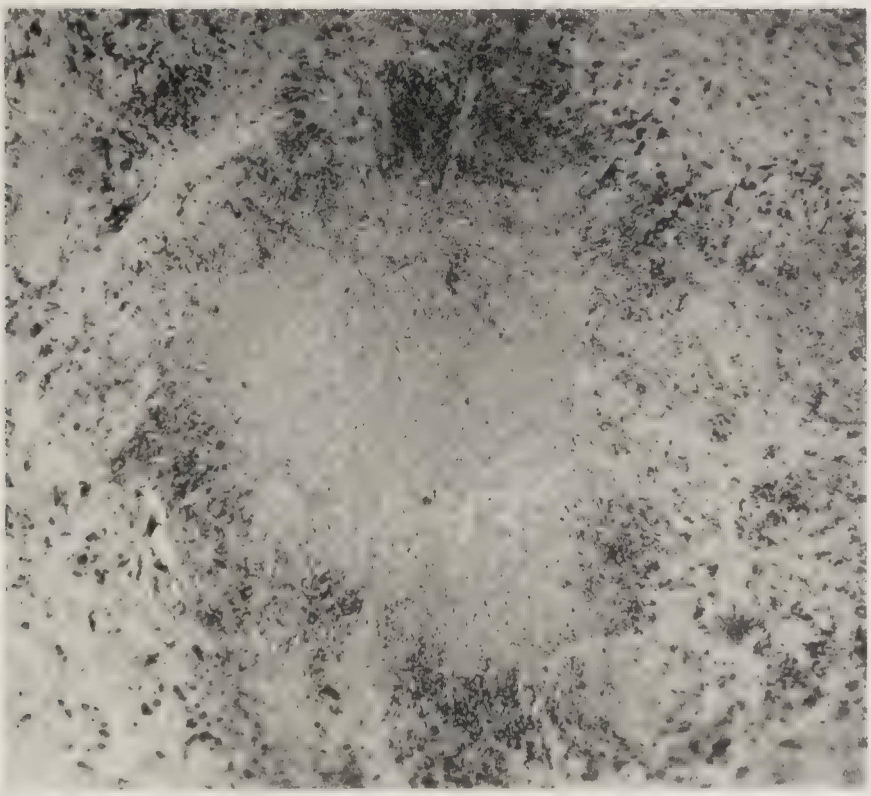

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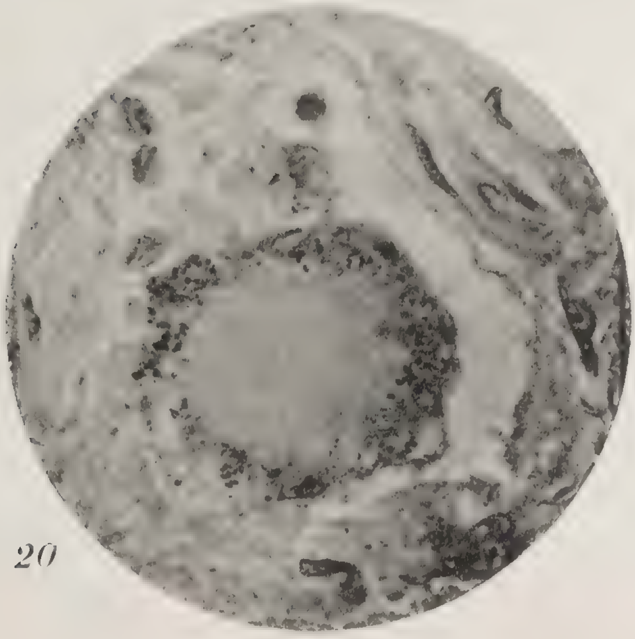

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TUBERCULOSIS OF THE LARGE ARTERIES

With the Report of a Case of Tuberculous Aneurysm of the Right Common Iliac Artery

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TUBERCULOSIS OF THE LARGE ARTERIES

WITH THE REPORT OF A CASE OF TUBERCULOUS ANEURYSM OF THE RIGHT COMMON ILIAC ARTERY*

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Tuberculous lesions of the vascular system have long been of interest as points of distribution of bacilli in cases of general miliary tuberculosis. The following example of such a lesion is noteworthy for two reasons: first, on account of its rarity; second, because it gave rise to the presence of great numbers of tubercle bacilli in a few glomeruli in the kidney, where they caused little or no reaction in the tissue about them. Weigert, as early as 1877, pointed out the important relation between tuberculous lesions of the vascular system and general miliary tuberculosis. Following his papers a very large literature has grown up on the subject. All manner of tuberculous vascular conditions have been carefully studied and described. These have included lesions of the thoracic duct, pulmonary and systemic veins, large and small arteries, and even of the heart itself. Commonest of all are the lesions of the veins and especially those of the pulmonary veins, while those of the aorta and its main branches are exceedingly rare.

Four general types of tuberculous lesions of the aorta and its main branches have been described: (1) miliary tuberculosis of the intima; (2) polypi of tuberculous tissue attached to the intima; (3) tuberculosis of the wall, involving the several layers; and (4) aneurysms, the walls of which are composed of tuberculous tissue.

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* Reported from the Pathologic Department of Harvard University.

The first-mentioned class, that of miliary tuberculosis of the intima, is by far the most common type recorded. It is most often described as occurring alone, but has also been found as an accompaniment of the other forms mentioned. Benda and Geisler[1] reported an exceedingly interesting example, in which not only the intima of the aorta, but also that of the iliacs and femorals were covered with bright, glistening miliary tubercles. Thorel[2] had a case with extensive involvement of the intima of the aorta. Other well-marked cases have been given by Hanot,[3] Schudardt,[4] Weigert,[5] Marchand and Huber,[6] and others.[7]

Examples of the second type have been placed on record by Benda,[8] Stroebe[9] and Aschoff.[10] The lesion consists of a small pear-shaped mass of tissue, which resembles a white thrombus in appearance, and is attached by a pedicle to a slight elevation of the intima, with the distal portion swinging free in the direction of the blood-current. In Benda's two cases the attachments of the polypi were over old atheromatous areas. Benda thought that tubercle bacilli from the blood had been implanted on the old sclerotic patches and that this was followed by thrombus formation over the area, which later became partially organized and assumed its polypoid form through the constant pulling of the circulating blood. In one of his cases the polyp reached a size of 1.2 cm. in length. Microscopically the polypi are seen to be partially caseous and to contain numerous tubercle bacilli.

Under the third heading are included all tuberculous lesions affecting the several layers of the wall. Ditt-

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rich[11] reported a case in which the tuberculous process spread from a near-by caseous lymph-node and invaded in turn all of the layers of the aortic wall; a thrombus was attached over the point where the intima was affected. Buttermilch[12] had a case which came in a similar way from a tuberculous process in the vertebral column and brought about the formation of a nodule of tuberculous granulation tissue in the media, which pushed up beneath the intima and encroached on the aortic lumen. Hedinger[13] and Schwalbe[14] have also reported cases in which tuberculous granulation tissue has destroyed parts of the aortic wall.

Of the fourth and last group I have been able to find only four recorded cases and for the sake of comparison with my own case, it will be necessary to go somewhat more fully into the description of each case.

Kamen[15] described an aneurysm of the ascending portion of the aorta just above the aortic cusps. The patient was a soldier 24 years old who had chronic pulmonary and acute miliary tuberculosis. Death occurred from rupture of the aneurysm. The outer portions of the wall were in contact with a caseous lymph-node of the posterior mediastinum and showed advanced tuberculosis. The aneurysm was of the dissecting type and its cavity communicated with the lumen of the aorta through a tear in the intima.

Hannau and Sigg[16] reported a case of an aneurysm of the thoracic aorta arising in connection with a tuberculous lung cavity. The entire wall became replaced by tuberculous tissue. The cavity was filled with a caseating mass of thrombotic material.

Ribbert[17] demonstrated a specimen, from a woman 46 years old who died of chronic pulmonary tuberculosis, in which communication had been established between the lumen of the aorta and a cavity lying in a large tuberculous mass, which arose from the periosteum of the vertebrae. The outer layers of the aorta had been destroyed and replaced by tuberculous tissue and the process had advanced until rupture of the intima had occurred. A small oblique tear of the intima opened into a short canal which led from the aorta into the cavity. The cavity itself was nearly filled with caseous clot. As he points out, this was not a true aneurysm although the circulating blood passed in and out of the sac.

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[16] Hannau und Sigg: Beiträge zur Lehre von der akuten Miliartuberkulose, Mitt. a. klin. u. med. Inst. der Schweiz, Series 4, iv, 1896.

[17] Ribbert: Mitteilung über ein tuberkuloses Aneurysma der Aorta, Sitzungsb. d. nied.-rhein. Gesellsch. f. Nat.- und Heilk. zu Bonn, med. Section, May 14, 1910.

Councilman and Mallory[18] have given a very full description of the following case which occurred in a man who died of general miliary tuberculosis, affecting practically all of the organs. Old fibroid and calcareous nodules and large conglomerate tubercles were also found in the lungs. The entrance of the aneurysmal sac was seen as a small opening, resembling the exit of an artery, situated on the anterior surface of the lumen of the aorta 6 cm. above the celiac axis; it admitted a probe for a distance of 2 mm. From the outside the sac appeared as a spheroidal mass, measuring 1 cm. in its transverse and 0.6 cm. in its longitudinal diameter. The surface was smooth, reddish-grey in color and showed several whitish streaks. On the intima of the aorta beneath the opening were many miliary tubercles. A few scattered tubercles occurred lower down.

Microscopic sections of the aneurysm showed short depression in the wall of the aorta; a cleft at the bottom of this opened into a wider space, which in turn extended into a cavity, probably beyond the adventitia. The intima appeared to pass down through the cleft as a covering for the broken ends of the media and then became lost in the necrotic contents of the cavity. Between the intima and the media, there was a small focus of caseation necrosis. The media for the greater part appeared normal up to the place of rupture. The break was sharp and oblique. The broken ends of the elastic fibres were plainly seen. The outer layers of the media had undergone caseation necrosis. The adventitia was normal up to the point where it spread out into a mass of thickened connective tissue which lay on each side of the cleft, and portions of this were caseous and necrotic. The cavity was lined with fibrinous, partially caseous, hyaline material on the inside of which was a small irregular thrombotic mass, composed largely of dead cells and well preserved polynuclear leukocytes and endothelial cells. Stains for tubercle bacilli demonstrated the presence of great numbers in the thrombotic material.

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[18] Councilman and Mallory: A Study of Lesions in Selected Autopsies, Med. and Surg. Rep. Boston City Hosp., 1896.

The question of the process of development of tuberculous lesions in the arteries has given rise to considerable discussion. One school headed by Benda asserts that in the large majority of cases the lesions arise from direct implantation of the bacilli on the intima. In support of this theory they cite the facts that lesions have been found affecting the intima and not the media; that such lesions have often had their beginnings on old atheromatous ulcers which were not in themselves tuberculous; that in some cases in which more than the intima was involved there was no near-by focus, and further that in some of these latter instances tuberculous processes have been found in the thoracic duct or pulmonary veins, showing another point of entrance for the bacilli into the blood. Weigert[19] and his pupils, on the other hand, believe that the lesions come only from without and that the bacilli are implanted either by direct extension to the adventitia or through the vasa vasorum at the site of the disease process. Chiari, who made as complete a study of these conditions, perhaps, as has yet been made, concludes that they develop in all three ways, and vary in the individual cases.

The instance which I am reporting was obtained from an autopsy done at the Boston Municipal Tuberculosis Hospital at Mattapan. I am indebted to Dr. Francis P. McCarty for the clinical data. For the sake of brevity the history had to be considerably shortened, and only the most pertinent facts retained.

REPORT OF CASE

Patient.—F. J. Mc., man, aged 33; porter. Clinical Diagnosis: General miliary tuberculosis; chronic pulmonary and right-sided renal tuberculosis; tuberculous enteritis and aortic aneurysm.

History.—Patient had been twice married and had five living children. The first wife and one child died of tuberculosis. The patient was treated fifteen years previous to present attack for pleurisy with effusion. Two years before he had right testis removed at Massachusetts General Hospital, and a report of tuberculosis was returned from the laboratory. The patient made a good recovery and worked up to one month before death. He gave history of having received a kick in the abdomen by a horse five years previous to entrance to hospital. On entrance to the hospital, patient gave history of diarrhea for the past six months; of having lost 20 pounds during the last three months; and of bloody sputum for the last month. He was short of breath, had a severe cough and an elevation of temperature toward evening. He complained of a painful dryness of the throat.

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[19] Weigert, C.: Fall von Venentuberkulose Sitzungsb. d. schles. Gesellsch. f. vaterl. Kultur, July 13, 1877.

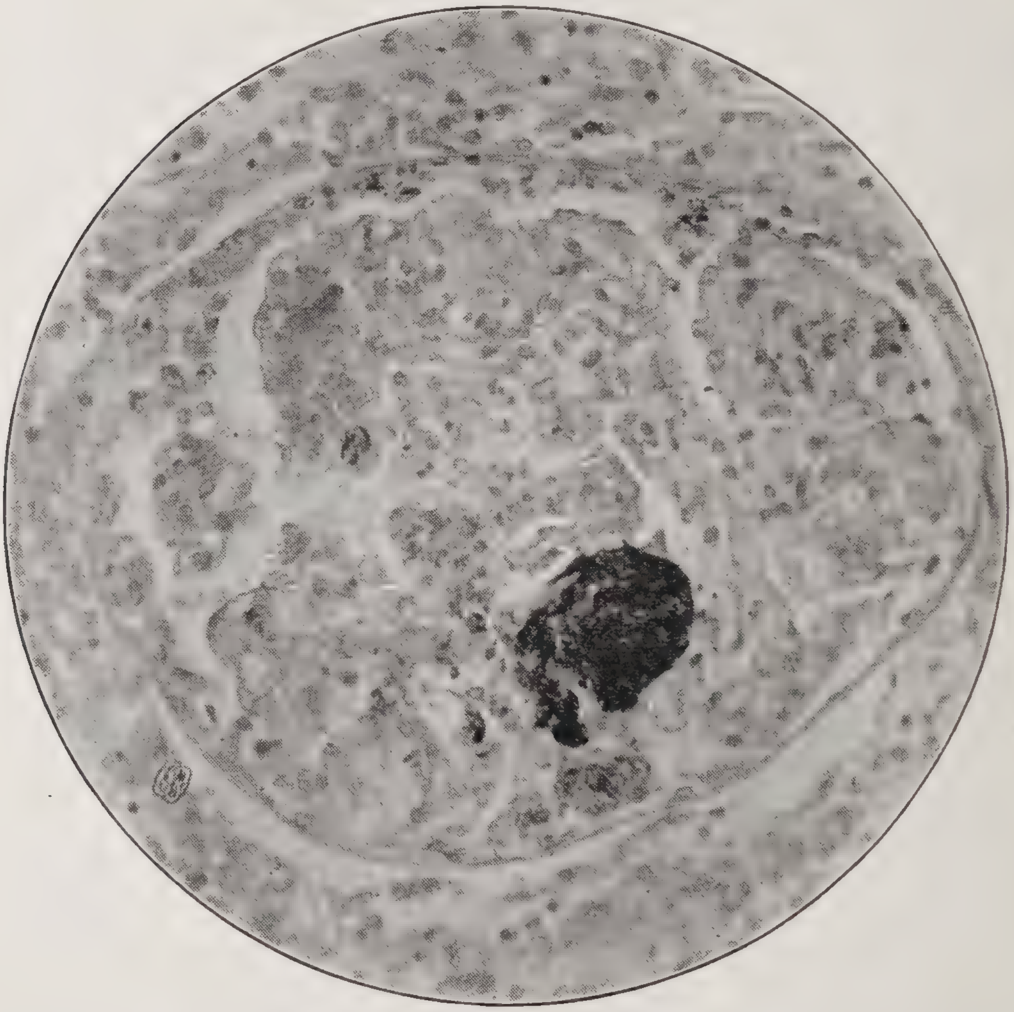

Fig. 1.—Masses of tubercle bacilli in the glomerulus of the kidney without inflammatory reaction about them.

Examination.—There was dulness of both apices which extended on the left side to the third rib, and on the right to the second rib in front, and to the lower border of the scapula in the back. The throat was deeply fissured and dry, but not ulcerated. The right testis was missing; the left apparently normal. A pulsating area about the size of a walnut was found somewhat to the right and below the umbilicus and over it a systolic bruit was heard. The liver was greatly enlarged and the right kidney was palpable, movable and tender. The clinical laboratory reported many tubercle bacilli found in direct smears from the sputum, feces and urine. The urine showed a specific gravity of 1.012, was acid and gave positive albumin and negative sugar reactions. The sediment contained many granular casts and pus-cells. There was a white blood-count of 15,000; a differential count was not made.

On the day before death, the patient developed marked dyspnea, moist râles in the right base and hyperresonance anteriorly. Miliary tubercles were observed on the back of the throat.

Necropsy.—At necropsy the examination was limited to a 15 cm. abdominal incision, so that the aneurysm and most of the other organs could not be observed *in situ.* There was no swelling or other external means of determining the location of the pulsating area observed on clinical examination.

Aneurysm: In front of the right common iliac artery a smooth spindle-shaped enlargement was felt. It was so densely adherent posteriorly that it was torn when it was removed. It was found to be covered with peritoneum, free from adhesions on its anterior surface, and covered with dense fibrous adhesions posteriorly, which gave it a ragged appearance. It measured 7 cm. in length, 4 cm. in breadth and 3 cm. in thickness. Its wall appeared to be continuous with the common iliac above and with the internal iliac below. The external iliac came off from the lower portion of the mass posteriorly. On opening the vessels, the enlargement was found to contain an aneurysmal sac, the cavity of which communicated with the lumen of the common iliac artery through an opening on its anterior wall, just above the division into internal and external iliacs. The opening was nearly 2 cm. long and 0.8 cm. wide. The interior of the sac was almost filled with reddish-grey thrombotic material which appeared caseous. This material presented a smooth surface which came directly in contact with the circulating blood.

Microscopically the outer wall of the sac was found to be continuous with the adventitia of the common iliac above and with that of the internal iliac below. It contained large masses of caseous material. The media and intima took no part in the enlargement. They continued unbroken until at a point about 2 cm. above the tear the outer elastic fibers of the media began to turn into the contents of the sac.

From this place on, the media became gradually thinner until at the point of rupture it was only about half its original thickness. The broken ends of the elastic fibers of the media were turned completely back on themselves and spread out in the caseous contents of the sac. The intima was thickened just above the break. It followed the inner fibers of the media outward through the opening and became lost in the mass of caseous material. The cavity was filled with lamellated thrombus, which still gave the fibrin reaction, though it was for the most part in an advanced stage of caseation necrosis. In the section taken from the upper lip of the tear there was seen a polyp-like piece of clot, which extended into the cavity and must have partially occluded the opening during life. The remaining portion of the surface of the clot was smooth. Great numbers of acid-fast bacilli were found diffusely distributed in the polypoid piece of clot and throughout the entire contents of the sac. There were also clumps of these bacilli so large that they appeared as red blotches under the low power. They resembled colonies from pure cultures of tubercle bacilli. In a section taken from the lower portion several small lymph-nodes containing areas of caseation were seen lying between the internal and external iliac arteries.

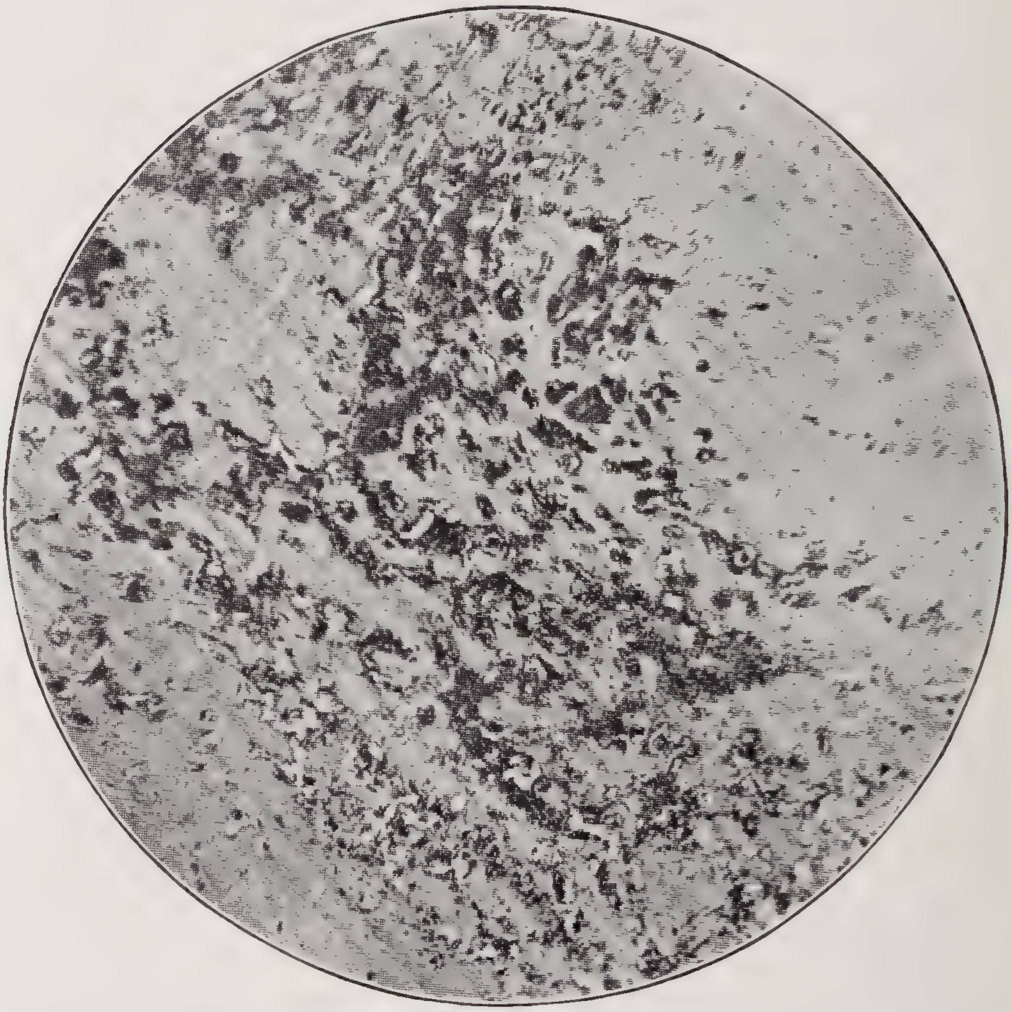

Fig. 2.—Masses of tubercle bacilli in the caseous clot in the aneurysmal sac.

Kidneys: Together the kidneys weighed 450 gm. They presented granular surfaces, swollen cortices, fatty streaking of the medullae and a moderate number of caseous tubercles. Microscopically some of the glomeruli of the kidney were filled with clumps of acid-fast bacilli. About these there appeared no evidence of reaction, either inflammatory, proliferative or necrotic. The capillaries of these glomeruli were simply dilated and filled with masses of red-staining bacilli. In one or two instances simple proliferation of the pericapsular endothelial cells of the glomerulus was observed. The proliferating cells contained similar bacilli. There was here no suggestion of exudation. Many early tubercles without caseation were seen in the kidneys, some of them bearing a definite relation to glomeruli. Older lesions were present but not numerous; they were caseated single and conglomerate tubercles.

Lungs: The left lung was covered with old fibrous adhesions. Beneath the pleura could be seen and felt many small, firm white nodules varying considerably in size. In the upper lobe was a small thin-walled cavity 3 cm. in diameter. The cut surface presented tubercles varying in size from the finest glistening points to a diameter of about 3 mm. In the upper lobe were several foci of caseous consolidation. The right pleura showed a single band of apical adhesions and was otherwise free. The right lung contained no cavities. Many minute tubercles were seen on the cut surface. The greater portion of the lower lobe was consolidated and scattered over with yellowish tubercles. Microscopic preparations from the lungs showed typical tuberculous lesions ranging from the earliest endothelial proliferations without caseation to old conglomerate tubercles. Sections were also made to confirm the tuberculous nature of the pneumonic areas and of the wall of the cavity. Stained with Ziehl-Nielson's method the sections showed enormous numbers of acid-fast bacilli.

Other Organs: The spleen weighed 300 gm., was enlarged, congested and contained many finely granular tubercles. The liver weighed 2,275 gm., was enlarged, fatty and contained many tubercles, some of which were caseous. The intestine and urinary bladder showed ulcerations. The right seminal vesicle and prostate contained caseous material. The heart, aorta, stomach, pancreas, gall-bladder, adrenals, left testis, epididymis and seminal vesicle were negative.

All of the gross lesions described above were verified microscopically.

In spite of the fact that no cultures were made in this case, we concluded that we were dealing with tubercle bacilli because the lesions were typical of tuberculosis in every way, and the organisms, so far as morphology, staining reactions, and distribution were concerned, were identical with those of the tubercle bacillus in acute miliary tuberculosis.

It seems that in this case the process leading to aneurysm came from without, but since the attachment to the vertebral column could not be seen we do not feel certain whether it came from a caries of the bone or from tuberculosis of some of the surrounding nodes. Neighboring tuberculous lymph-nodes were found but the lesions in these might have been secondary and not primary. The important evidence then lies in the facts that the more advanced lesions were in the adventitia and the outer layers of the media, while the inner layers of the media and the intima showed only the effects of rupture. The history of the kick was ruled out as a possible cause on the ground that the aneurysm was protected on all sides from direct injury by the bony pelvis.

We believe then that the tuberculous process spread directly to the adventitia of the right common iliac artery from some near-by focus; that it so involved the media as to lead to rupture; that the pressure of the blood pouring through the opening separated the inner layers of the media from the outer layers and the adventitia, thus producing a sort of dissecting aneurysm; that the blood in the sac thus formed underwent coagulation and became infected from the tuberculous adventitia, and served as a medium for the growth of the tubercle bacilli and as a source of constant supply of them to the blood. In this way the marked variation in the age of the miliary tubercles of the organs is satisfactorily explained.

The presence of tubercle bacilli in the glomeruli of the kidney without inflammatory reaction, we think, indicates that the patient had reached a stage in which his system of defense — call it "immune bodies" or "what not" — was so exhausted that it could no longer react against the stimulus of the toxins of the tubercle bacillus. This we believe to be analogous to those cases of advanced tuberculosis and miliary tuberculosis in which the tuberculin reaction fails.

In other glomeruli, the multiplication of the pericapsular endothelium containing tubercle bacilli, we believe to be definite instances of simple endothelial proliferation, without exudation, due either to the toxin or the presence of the tubercle bacilli.

In closing I wish to express my indebtedness to Drs. Councilmann, Mallory and Klotz for their help and suggestions in the preparation of this paper, and to the former for the use of the pictures.

THE LIFE AND WORK OF ROBERT KOCH.

By

I.N. Pochapin.

The development of Bacteriology into a real science, has been the founda-of most of the progress made in medicine and surgery, during the past quarter of a century. In this advance, no name occupies a more illustrious and honored place than that of Robert Koch, who developed and elaborated the theories of Lister and Pasteur, as well as many others, and vastly improved the methods and technique of Bacteriological investigations until it has become the real science of preventive medicine.

Koch's entire life has been given to pains-taking and persevering, but bold and original researches in medicine. Such untiring activity in the promotion of the progress of science was well repaid, when we think of the numerous achievements in the various branches of medicine directly or indirectly traceable to the discoveries of this scientist. No praise bestowed upon Robert Koch by his ardent followers and admirers is too extravagant, when we remember that every well trained physiciah and surgeon of the present generation uses in his daily work the knowledge which has come as the result of the investigations of Koch; that every properly organized medical and hospital has a laboratory founded on the methods which Koch devised, and the apparatus which he invented; that every

*Read before Sophomore Class-
November 1913.

municipality in the fight against the great pestinences of the world, cholera tuberculosis, typhoid fever, diphtheria, and in the efforts to provide for its citizens' food which cannot serve as the vehicle of infection, depends for its preventive measures upon the doctrines which Koch proved.

An inquiry into the circumstances of Koch's life, and a careful analysis of his environment may determine the reason why he occupies such a pre-eminent place in medical science.

Robert Koch was born in Klausthal in the province of Hanover on December 11, 1843. Koch's family had lived in Klausthal for a number of generations and had been for some years in the employ of the government. His father was a man of considerable scientific attainment, whose reputation spread beyond the little district in which his activities were centered, and who was honored by the Prussian Government with the title of expert mining engineer. Koch himself was one of eleven children, two daughters and nine sons. His mother was a hard working woman whose domestic cares and responsibilities prevented her from devoting much attention to the rearing of her numerous progeny, and his father from the nature of his work, was compelled to absent himself from home during much of his time. Koch was consequently

left to grow up in a crowd of wild and untrained boys. He attended the Klausthal gymnasium in which the instruction was poor and the discipline lax. He took an active part in the school life; he was an excellent athlete; a member of a school society, and also a member of the glee club. During this time his chief outside occupation was with his father whom he accompanied on long walks over the hills and valleys of the surrounding Harz country. He early showed a passion for natural science and made numerous collections of minerals, plants, and small animals, His reading along lines of geology and botany as well as zoology was extensive and during his entire life and work he kept up this active interest in the branches of learing collateral to the science of medicine.

In the year of 1862, Koch left the Klausthal Gymnasium, wended his way to the University of Gottigen and entered upon the study of medicine. The faculty of the university then included a number of men who left their marks on science. The senior among them was the chemist Friedrich Woeler, who in 1828, accomplished the synthesis of urea. Others were the pathologist Wilhelm Krause and the physiologist George Meisner. The most important man, however, was Jacob Henle, whose scientific work and mental grasp were so wide that his

writings covered the field of physiology and pathology as well as anatomy.

In the year 1865, after receiving a prize for a thesis about the ganglionic cells and uterine nerves, Koch was appointed assistant in the pathological museum of Which Krause was the director. This appointment offered him the opportunity of acquiring a thorough training in pathological and microscopical technique, a training which aided him greatly in his future work on microorganisms. At the same time Koch served as an assistant in the physiological institute under the direction of Meisner. While making a study of the excretion of succinic acid in animals fed exclusively on meat and fat,Koch was unwilling to limit his observations to the lower animals, but endeavored to work out the problem upon himself. He ate half a pound of butter daily and estimated his output of succinic acid. He undertook these experiments in the hot days of summer and after five administrations of this fat-rich diet his stomach revolted, he developed a violent attack of gastric catarrh and was compelled to finish his work upon the less sensitive animals.

In January, 1866, Koch finished his academic career passing the examinations with the mark cum laude. In March of the same year he passed the state examination in Hanover, and became an assistant in the General Hospital in Hamburg for a short term of three months, and in October took a place as physician to the Asylum for Idiots in Langenhagen. In 1869, he moved to Rakwitz in the Province of Posen. From Rakwitz he enlisted as a surgeon in the Franco-Prussian War and after his return in 1872, secured the position of district-physician in the town of Wollstein.

In Wollstein Koch remained for years busily engaged in a general country practice of medicine. Although he was out of touch with university affairs which he loved, yet from the time of his arrival in Wollstein he occupied himself unceasingly in attempts to solve the most important questions in medicine of his day. He fitted for himself a laboratory, purchased a microscope and installed a thermostat which could be kept at body temperature. He devoted all his spare time to the study of a disease of animals widely spread in the district where he lived.

Contrary to the natural course of human endeavor along the line of least resistance, Koch did not lapse into the respectable mediocrity of his surrounding environment, but pressed on in the search of knowledge with ever increasing ardor. This peculiar adaptation of Koch, in the absence of the circle of intellectual activities, which is a stimulus to great endeavor, becomes clear when viewed in the light of his early training and university associations. It was due to his former activity that he did not allow the routine of a country practice to swamp his intellectual aspirations, but kept his fingers busy with slides and coverslips, and his eyes glued to the microscope in all the spare hours which he could snatch from his exacting duties.

Koch's first publication appeared in 1876 when he was thirty-three years old and ten years after his graduation from Gottingen. In a paper of over forty pages, Koch described with great exactness the many experiments he had conducted upon the organisms of splenic fever, the methods he had employed, and the conclusions which could be drawn from his work.

The complete life cycle of the B. Anthrax was worked out, and for the first time in the history of bacteriolbgy a pathogenic microorganism was cultivated artifically in pure culture outside the animal body and the specific disease produced. He made a careful study of the natural disease in cattle, sheep and horses, and produced the disease artifically in mice and rabbits by inoculation with blood or with splenic pulp from infected animals. He settled absolutely the etiological relationship of the bacillus of anthrax to the disease.

In November 1877, Koch published his second paper. Here he described his method for making films of bacteria on the surface of coverslips, fixing them by gentle heat, and his application of the aniline dyes for the demonstration of bacteria in tissues in order to the study of these bacterial films. The bulk of this paper, however, is given up to the subject of the photography of bacteria.

The work of Koch was accepted everywhere in Germany, but met with some opposition in France. To disprove the claims of his opponents and to throw more light upon the etiology of infectious

diseases, Koch had been putting his theory to a practical test and in 1878 he published his third paper entitled "Researches on the Etiology of Infected Wounds." In this paper Koch puts forward clearly the exact state of knowledge on the subject of surgical analogous conditions in animals resulting from the subcutaneous injection of putrid material.

Koch's growing reputation prevented his longer sojourn in Wollstein and his admirers procured for him the position of Municipal physician in the city of Brealau. After staying only three months in Brealau, Koch retraced his steps to Wollstein where his old place was still unfilled. Koch, however, was now much too big a man for this little community and was soon called away to Berlin where, through the instrumentality of Cohnheim, he was appointed member of the health bureau. From this time on Koch devoted himself exclusively to laboratory work. At the end of the first year he published his observations in the Journnal of Royal Bureau of Health. In the first paper of this volume, Koch described his poured-plate method for the isolation of organisms in pure cultures. In order to accomplish this he used nutrient gelatin. THis material had previously

been employed in the cultivation of microorganisms, but only in solutions so dilute as not to harden and furnish the transparent medium which Koch desired for the study of his colonies. Simple as the poured-plate method appears to us at the present time and clear as are the various steps taken by Koch in the solution of the difficulty, it still remains for us the only practical procedure for obtaining pure cultures of microorganisms.

The end of the year 1881 may be said to mark the close of the inventive or constructive period of Koch's life. In the decade from 1872 when he returned from the Franco-Prussian War, to the year 1882, the science of bacteriology had changed from a chaos of conflicting views and observations to a well ordered system From this time on the work of Koch and his pupils was largely the application of the methods already perfected to the study of the etiology of infectious diseases.

In 1882, Koch worked out the etiology of tuberculosis by his discovery of the tubercle bacillus. He had observed the bacillus in pulmonary tuberculosis, cheesy bronchitis and pneumonia, tubercles of the brain, intestinal tubercles

and fungous inflammation of the joints. He supposed that, escaping into the air from the expectorations of phthisical patients, they were inhaled into the lungs, where they developed. This deductive reasoning of Koch is important inasmuch as it shows that he was pursuing the truthful path of bacteriological research at a time when spontaneous generation was yet the much discussed topic of scientific controversies. In this communication, Koch seems for the first time to have clearly formulated in print the laws which are known by the name of "Koch's postulates."

In 1883, Koch was made the head of the German Cholera Commission and went first to Egypt and then to India. His report on the subject was published in the Klinishe Wochenshrift of Berlin. He had found in the dejecta of patients suffering from cholera, besides the micrococci and bacilli common to the evacuation of other patients, peculiar, curved bacteria, which have become known as the comma bacilli. Koch declared that these bacilli are the cause of cholera, maintaining that the natural history of the disease corresponds with the various characteristics of

the organism in question. Of special importance from the public health standpoint was his cultivation of the vibrio from drinking water and from articles of food. On Koch's return from India, he was given a donation of 100,000 marks by the state.

In 1885, Koch became Professor of Hygiene and Bacteriology in the University of Berlin, a chair with this title being created for him. Koch now became the center of scientific attraction and his laboratories were crowded with men from over all the world anxious to learn the new methods and technique. In the list of students who worked with Koch are many of the foremost investigators of the present day, included among the number being Gaffky, Loeffler, Wassermann, and many others.

It is significant that the etiology of many of the infectious diseases which we now understand was solved by Koch or his pupils. Thus to Koch himself must we credit anthrax, tuberculosis, cholera, infectious conjunctivitis, to Gaffky typhoid fever, to Loeffler diphtheria and glanders. In many other instances the methods which Koch devised, when adopted by his followers over all the

world have brought solution to problems of the greatest importance in medicine and surgery.

In 1891, Koch became Director of the Institute for Infectious Diseases in Berlin, which was built under his special direction. Here he remained as Director till 1904, when he was relieved at his own request, his place being taken by Gaffky. From 1904 he was honorary member of the Institute and continued there his active investigations. During this period he was constantly engaged in the study of the infectious diseases and was especially concerned with the problem of devising the proper measures to limit their spread. Due to his discoveries, it was possible to check the great cholera epidemic in Hamburg in 1892, and the following year he pointed out how clearly many of the great epidemics could be traced to polluted water, advocating water filtration as the best means of preventing its dissemination by this path.

In 1896 he went to South Africa and Cape Colony to study rinderpest. He devised a method of preventive inoculation to control this disease and spent some time there in the study of the protozoon

parasites. Upon his return to Berlin he published the results of his investigations upon Texas fever, tropical malaria, rinderpest and bubonic plague.

In 1900 he gave his famous London address on tuberculosis, in which he modified the views originally expressed as to the idenity of bovine and human tuberculosis and maintained that no great danger exists of the transmission of the animal disease to man. The decade which has passed since the time of his address, has served only to demonstrate the correctness of Koch's views that our greatest efforts should be directed towards preventing infection from pre-existing cases of human tuberculosis.

The latter part of Koch's life was rather sad. Bitterly disappointed in the failure of tuberculin to become the great healing remedy, adopting in his family a course of conduct which alienated him from many of his friends and apparently robbed him for some time of some of those official honors which his scientific attainments had merited so long, gradually losing his strength and suffering from infirmities, the great scientist was a somewhat pitable figure. In March 1910, he

began to suffer from cardiac distress, but refused to give up his work at the Institute, where he labored daily from nine in the morning till half-past two in the afternoon.

On April 9th, he had a sudden attack of heart failure in the night and was saved only by the use of the strongest stimulants. His strength, however, was somewhat greater than either he or his physicians anticipated and he recovered sufficiently to sit up in a wheeled chair and receive the visits of his devoted friends. In his modest apartments surrounded by his collections of minerals, plants and animals, his chief delight was talk of the science to which his life had been devoted. His strength revided sufficiently for him to be removed to Baden-Baden, where it was hoped that the clear balmy air might assist his recovery, but his race had been run and he died Friday, May 27, in the 67th year of his age.

There have, no doubt, been many discovers as great as Koch, but it is seldom that one has been so individually associated with the development of science. And today, when we reflect upon the development of Bacteriology made possible by Koch's discoveries, the consequent revolutionary changes in surgery and medicine where by means of knowing the principles of infection and immunization, which were first conceived by Koch, we can not only cure disease but prevent its oncome, our admiration for the man who made all this possible reaches its highest expression. "No disease without a germ" is a living monument which the scientists of today have erected in the memory of "The Father of Bacteriology."

Degeneration of the Nucleus Lentiformis Associated with Cirrhosis of the Liver.

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Under the title of "Progressive Lenticular Degeneration", S. A. K. Wilson has recently described a series of cases presenting a peculiar symptomatology and revealing at necropsy characteristic lesions. For a detailed description of the disease the reader is referred to his papers[1], but the important features are described below.

The disease is "familial in the sense that it frequently attacks more

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[1] Lancet, Apr. 27, 1912, p. 1115; Brain, vol. xxxiv, p. 295.

than one member of a family, but is neither congenital or hereditary." It always occurs in young people and is invariably progressive and fatal. The symptoms form a characteristic syndrome. They are: (1) bilateral involuntary movements of the extremities, sometimes also of the head and trunk, of the nature of a rhythmical tremor, increasing with volitional movement; (2) pronounced spasticity, or rather hypertonicity of the musculature, generally the face being set in a spastic smile, while the limbs are in contracture; (3) in the later stages of the disease true contractures set in; (4) dysphagia and dysarthria due to rigidity of the corresponding muscles; (5) a degree of emotionalism, the patient responding abnormally to slight stimuli; (6) there is little or no true paresis or paralysis, the patient being able to

perform ordinary movements at all joints, although slowly or feebly- the reflexes are intact; and (7) transitory mental symptoms are present in some cases. The symptoms are, therefore, of a motor nature, and are extrapyramidal in origin. This symptom-complex, Wilson believes, constitutes The syndrome of the corpus striatum.

The morbid anatomy is no less characteristic than the symptomatology. There is a bilateral symmetrical softening of the nucleus lentiformis associated with cirrhosis of the liver. The softening affects the putamen, and to a less extent the globus pallidus. The caudate nucleus, optic thalamus, and internal capsule are not involved. The disease commences apparently around the lenticulo-striate vessels, as a result of

which the lenticular nucleus begins to shrink and atrophy, the laminae medullares and internuncial fibers become less and less recognizable, while the nerve cells disappear and neuroglial overgrowth takes their place, but it in its turn tends to break down, so that in advanced cases softening and cavity formation are the result. There is no sign of syphilitic disease of the blood vessels, all of which are patent. Occasionally petechial haemorrhages occur. Even where the cavity formation is advanced there is no evidence of obliterative endarteritis; on the contrary, the vessels are sometimes thin, fragile, and hyaline-looking. The internal capsule in an uncomplicated case is intact.

The cirrhosis of liver is an essential part of the morbid anatomy, being constantly present. It is peculiar in that

it produces no symptoms during life. The cirrhosis is of a mixed type. It is principally multilobular, in some places being monolobular and occasionally there are indications of intralobular cirrhosis. In the liver substance normal areas, necrosed areas, areas of fatty degeneration are found to be scattered irregularly through the organ. Syphilis and alcohol appear to be definitely excluded as factors in the production of this cirrhosis.

Wilson was able to collect 12 cases. Six had been previously reported, 2 by Sir. W. Gowers in 1888, 1 by Omerod, and 3 by Homen in 1890. Wilson personally observed 4 cases and obtained the unpublished records of 2 others. Necropsies were obtained in 10 of these 12 cases; in 3 of the older cases no definite findings

in the central nervous system are reported, but in the other 7 cases various stages of the lesions described above were constantly present.

Since the publication of Wilson's paper, two more cases have been reported, one by L'Hermitte[2], and one by Yokoyama and Fischer[3]. The fomer occurred in a boy 11 years old, who suffered principally from motor disturbances in the domain of the bulbar nerves, dysphagia, dysarthria, and a spastic smile. There were occasional spasmodic contractions of the muscles of the face, and the arms became involved so that writing was impossible. Later the patient was reduced to a state of extreme helplessness by the spastic condition of the musculature generally, although true paralyses were absent. Finally, there occurred a mental

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2.Semaine Medicale,1912,no.11.
3.Virchow's Archiv,B.ccxi,p.305

deterioration and epileptiform seizures with marked emaciation. At the necropsy there was found a marked atrophy of the corpus striatum with degeneration of the putamen of the lenticular nucleus. The vessels were healtny. The liver showed a degree of cirrhosis evident to the naked eye. Microscopically the fibrosis extended from the portal spaces, cutting the liver substance into islands, sometimes of several lobules, at other into portions of a lobule.

The second case was less typical. The patient, a girl 19 years old, suffered from dementia and disturbances of speech and gait. Her illness extended over five years. At the necrosy the liver was found to be enlarged and nodular,the nodules being large and irregular in size, so that externally it resembled a

syphilitic cirrhosis. Microscopically, however, no evidences of syphilis were found. In the central portions of the nodules large necrotic areas surrounded by a haemorrhagic inflammatory zone were present. The brain showed a loss of nerve fibers with gliosis in the cortex, particularly in the frontal region, and the same condition, was to a lesser extent, present in the left lenticular and caudate nucleus. The right nuclei were not involved. There were no vascular changes.

The case here reported bears little clinical resemblance to those described by Wilson, but the necropsy findings of cirrhosis of the liver associated with bilateral symmetrical haemorrhages and softening of the nucleus lentiformis are interesting when considered in connection

with his reports. It was impossible to obtain a detailed history but the essential points are given. I am indebted to Dr. J. D. Heard for the clinical notes of the case. The patient was admitted to the medical wards of the St. Francis Hospital on Dec. 1, 1912. She was a corpulent woman, 53 years old and complained principally of general muscular weakness of some week's duration, apparent chiefly in walking; at times her knees gave way and she was afraid of falling. She also complained of dyspnoea and headaches for some weeks. She gave a marked personal and family history of alcoholism. There was no history of jaundice or ascites. On admission her mind was not clear, and during her stay in the hospital mental symptoms were almost

constantly present, she being commonly irrational, suffering from hallucinations, and at one time verging on delirium tremens. At times, she showed irregular purposeless movements of the hands, but marked tremors were absent. Towards the end of her illness the patient became extremely weak and helpless, voiding urine and faeces involuntarily. She had extreme dyspnoea with some cyanosis, and finally became stuporous. Physical examation on admission revealed little, save an enlarged liver. The temperature was normal except for a rise just before death. Lumbar puncture on Dec. 15th yielded a fluid under slightly increased tension. The Wassermann reaction was negative with both blood, serum and spinal fluid. Death occurred on Dec. 16, 1912.

At the necropsy the liver was found to be considerably enlarged, weighing 2170 grm. and measuring 26 x 22 x 10 cm. The lower border was covered by fibrous adhesions and was rounded. The entire surface was finely nodular. On section the liver was seen to be cut up into small nodular masses of fairly uniform size which varied from that of a match-head to a pea. These nodules bulged above the cut surface and were separated from each other by fine fibrous bands. The liver tissue throughout was of a pale yellow fatty color showing here and there a very slight amount of greenish bile staining. The gall bladder contained one large oval stone. The bile ducts were negative.

Sections of the liver showed a

general increase in connective tissue which was most marked about the portal systems. This fibrous tissue was fairly dense, although the individual bands were narrow. It showed in places a number of young connective tissue cells and there was a diffuse infiltration of lymphocytes throughout it. Within these bands of fibrous tissue numerous pseudo-bile capillaries were present. These bands of connective tissue tended to surround the individual lobules, although in places there were areas where the liver substance was subdivided by the invading connective tissue into islands of but a few cells each. The liver cells showed a most marked fatty change, but few cells escaping. Most of the cells showed clear, well-stained nuclei, and necrosis could

not be demonstrated. Externally the brain appeared quite normal, but on section there was found in each of the lenticular nuclei a small area about 1 cm. in diameter which showed numerous small punctate haemorrhages. These areas occupied the anterior portion of the putamen, in its outer and inferior parts, and were practically symmetricla. The tissue about the haemorrhages was paler, oedematous, and softened. These areas were confined entirely to the lenticular nuclei; the interal capsule appeared quite normal, the caudate nucleus and optic thalamus showed no change. The rest of the brain was completely negative. The vessels at the base of the brain were free from sclerosis.

Microscopically the lenticular nucleus showed the presence of many small haemorrhages around the capillaries. In

places the haemorrhage was quite extensive and was found to infiltrate the tissue at some distance from the vessels. The haemorrhage was of recent origin, and the red blood cells which had escaped were for the most part well preserved; no old blood pigment was noted. The haemorrhage was not accompanied by an inflammatory reaction. About the vessels, even in the absence of haemorrhage, the nerve tissue showed areas of degeneration, being more faintly stained, and having in general a rarefied appearance as though some of the fibers disappeared. The nerve cells showed degenerative changes in their protoplasm, some being vacuolated while others showed the presence of fine granules which stained deeply with eosin. There was no increase of glia cells. The blood-vessels were all quite healthy, and

it would appear that the haemorrhage was due more to loss of support from without than from actual disease of the vessel wall. The necropsy findings in the other organs were of minor interest and had no apparent relationship to the lesions described.

This case differs from those heretofore reported in that the patient was considerably older. None of the typical symptoms were present; however, the lenticular lesions were not advanced, and the rapid development of a profound toxic process may have masked or prevented the development of more characteristic symptoms. Her illness began with symptoms of a motor nature- namely, general muscular weakness with a tendency to fall when walking- but unfortunately we had no opportunity to study the case at this time.

It is difficult to say what causes the lenticular lesions. In the absence of an inflammatory reaction one thinks first of impaired nutrition, secondary to circulatory disturbances. The vessels, however, are entirely free from thromboses, emboli, or obliterative lesions; in fact, they appear quite healthy. It further becomes difficult to explain the degenerative changes on the ground of disturbances of circulation, when one remembers that the lenticular nucleus derives its blood supply from several sources. The earliest changes occur in the tissue immediately surrounding the vessels, and it is probable that there is some circulating toxin at work which has a peculiary selective action for these tissues.

The association of cirrhosis of the

liver with degeneration of the nucleus lentiformis in this disease is so constant as to leave, no doubt, that there is an important relationship between them. Concerning this relationship two hypotheses present themselves; first, that the same substance which produces the liver changes also affects the lenticular nucleus; and second, that there is elaborated in the diseased liver some toxic body which has a peculiar affinity for the tissues of the corpus striatum. In our own case there was a marked history of alcoholism, and the liver definitely showed an early stage of Laennec's cirrhosis. If it be granted that the lesions of the lenticular nuclei as here described are an early stage of the process described by Wilson, it would appear that the disease may be associated with other types of cirrhosis having a more

definite etiology. This would seem to indicate that our second hypothesis, already suggested by Wilson, is correct. If this be true, one would expect to find these lesions more frequently than has been heretofore reported.

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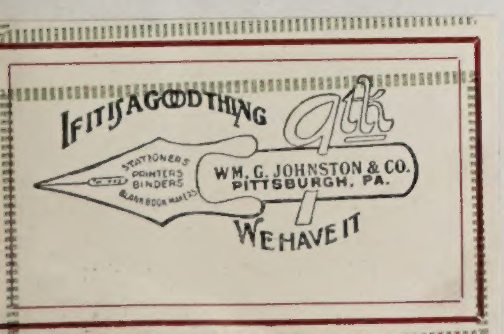
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